



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

29 June 2021

Meeting Minutes

Members

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CIOMS

Catherine Bates, Lembit Rägo

Regrets

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Introduction

Hervé welcomed the group and said he hoped members could meet in person, but this would not be before 2022. Lembit updated the group on CIOMS news, including a new working group which will begin in July and will focus on ethics in the area of research and will explore governance issues of research institutions.

The quarterly CIOMS newsletter will be issued shortly.

Regarding governance for the WG, Lembit put forward a proposal, which was subsequently accepted by the group, and that reflects a fair geographical representation between Asia, Europe and the Americas:

Chair: Hervé

Co-chair: Melissa

Co-chair: Chia-Yu

Then, Catherine provided a recap of key points from the subgroup discussion on May 17th.



Discussion

Serious vs Severe

Lesley began by asking about the serious vs severe given there is confusion around this. Hervé responded to say that he assumed the group would refer to “seriousness”, but the confusion arises as the result of the classification of side-effects that was created in the US many years ago. So, now one talks about “severity” rather than “seriousness”. He suggested that the group could refer to one or the other or both. The key is to be clear in the introduction. Lesley agreed and added that “severity” was broader than “serious” as not all events that are severe are serious.

Lembit recommended including both terms in the glossary to make it clear.

Alex asked if, from a mitigation management and diagnosis perspective, there was a difference between the two? Hervé responded that from a pharmacovigilance point of view, the goal of legislation is to mitigate the risk of serious adverse events, not severe. Alex felt that if the group plans to differentiate between serious and severe, the table of contents should be adapted accordingly.

Melissa confirmed that this was included in the table of contents and is part of the first section with the objective of trying to define it better. And added, that is where the group can contribute and explain that the terms are used differently in the clinical sense, which she felt, addresses Alex’s point, that severe disease might warrant a specific type of treatment depending on how medicine is practiced or managed. Whereas if something is “serious” in a clinical trial or in post-marketing, it falls under specific regulatory requirements, at least in the US, that [the event] must be reported within a certain timeframe. So, this was inserted in the introductory part of the table of contents.

Visual illustration of “severity” vs “serious”

Priya wondered if this could not be presented visually because, in a clinical environment and as a physician, one wants to manage the severity and prevent the event from becoming so severe that it ends up being serious. Then, once an event is serious, the regulatory reporting kicks in. Whereas, regulators want to reduce seriousness and come back to something that is less severe, so it is almost like two funnels that are joined together. If one could capture this visually, it might help bring the two worlds together. Hervé interjected to say that “severity” is not a pre-cursor to “seriousness”. One can have a condition that is serious up front, but it might not be severe. So, he did not see the link between the two with which Priya agreed, but stated that maybe a graphic could be included to represent these concepts visually.

Melissa supported the idea of providing a visual illustration because considering how broad the stakeholder audience is going to be, this might be useful. She was not sure exactly how to do this at this point, but liked the idea.

Case definition?

Looking at the diagnosis epidemiology description of adverse reactions, Priya asked if it was something like a case definition? She wondered if it was similar to the Brighton case definitions for vaccines? Does that give us something where people can make choices about what they see or what it is? Is it what we have to look out for when we do safety surveillance? Or is it exclusively for clinical management, which would be fine, too.



Hervé asked if the group was still discussing Catherine’s slides or had moved on to the table of contents.

Severe rather than serious

Ariel raised a question about DISSI and felt that this terminology sounded like it spoke more to regulatory authorities. To clinicians, when one mentions “serious”, it has regulatory undertones that point to hospitalization and fatality. Whereas SCARs and severe case adverse reactions are more all-encompassing. The term “serious” has regulatory connotations that not all audiences will understand.

Hervé agreed and said that he never uses DISSI. Ariel then asked if the group had an opinion about that. Alex suggested that from a clinical perspective, it won’t change anything and he didn’t know if seriousness for a skin event was any different from any other event. If Alex were to vote, he would favor severe skin injury and stay away from seriousness. Ariel concurred with Alex’s opinion. Siew also supported this view.

Siew further stated that serious means that it is potentially life-threatening or causes morbidity and is used in the context of pharmacovigilance. A condition can be serious if a patient has prolonged hospitalization due to the need for IV antibiotics, which is not severe, cause increased morbidity or mortality or is potentially life threatening, Severe would be better.

To Chia-Yu, “serious” is more of a pharmacovigilance term. Traditionally, we think that for skin symptoms, severe is sufficient to describe them, i.e. the body service area, the involvement of skin injury, the damage and extent of skin damage. “Serious” is the outcome, in pharmacovigilance terms, which shows the fatal or life-threatening outcome. So it depends. Chia-Yu stated and that he was open-minded. Overall, severe is more easily understood and more manageable from the clinical perspective. Whereas, for regulatory audiences, it would be better to speak of “seriousness”.

Hervé reminded the group that at EMA, there had been extensive discussions with Sabine Straus in the Pharmacovigilance Risk Assessment Committee (PRAC) and in the end, it was decided to adopt “seriousness” as a criteria. He stated that, CIOMS is independent, and can, therefore, decide to only keep severity, adding that this question needs to be resolved in order to move forward because it has implications in terms of diagnosis and management.

Priya suggested that given the publication’s focus on clinicians, she would recommend using terminology that speaks to them. She also put the suggestion to the group, that what it was looking at was “drug-induced skin injury of serious outcome”. It sounds like a different concept. Hervé concurred with Priya’s approach.

According to Ariel, there are already criteria for “serious” from a foreign pharmacovigilance perspective. He suggested that the role of the WG is to identify, clinical entities that could lead to a severe outcome, meaning as Siew said, there’s a life-threatening outcome, which, to him, means “severe”. “Serious” has specific implications and which would meet identified regulatory thresholds, e.g. hospitalization and death. Hervé reacted by suggesting that serious is a retroactive concept, something that is determined after the fact. But what catches ones attention is “severity”. He



referred to Priya's concept such that one could talk about a severe condition with a serious impact on the outcome or something along those lines. It's complicated to summarize this.

Maculopapular eruptions

Siew referred to the introduction, and asked if "severity" and "seriousness" would be defined based on pharmacovigilance criteria? What about a severe skin eruption? If a skin lesion is limited or not severe, let's say maculopapular eruption, how can one define it as severe? Is it based on a certain percentage of surface area? So the WG could keep non serious skin reactions which would be categorized as DISSI.

Hervé supported Siew's point, saying that with micro-maculopapular reactions, what is important is to have small eruptions, but with an underlying DRESS syndrome or a very severe maculopapular eruption with a very benign cause or something like this.

Neil introduced the idea that for an exanthematous rash, the biggest differentiator right from the start is fever. And if they have fever, it could be DRESS. If they don't, then not. It could be like penicillin or something like that and they have quite different outcomes. So there are criteria and the other criteria is a swollen face that we see with the fever in some of the DRESS patients and they have different outcomes. But fever is usually the best differentiator. If you're just seeing a picture and you say it's an example and it tells you nothing, you need to know a little bit about the patient. And to that the simplest thing is fever.

Hervé agreed, but asked about the definition of the skin reaction without any other context? What do you do? To this point, Neil put forward that if one is just seeing the skin, there is nothing one can do. "It's the end of the game". That's the problem. One has to get doctors and others to report their cases to understand the issues and exanthems are a good example. Whether it's pediatric, adults, seniors, one has to be able to do it-skin of color could be challenging-but one needs something else besides the picture.

Which words to use?

Melissa stated that with regard to the name, the reason the group came up with "serious" (the group also discussed "severity") was that at the time, the WG were focusing just on SCAR, which typically have serious outcomes, which is what clinicians would be most worried about. But, to regulators too, SCAR might be the biggest safety risk related to skin findings. So, Melissa didn't know if the group had come to an agreement about the name, because it seems the group is now moving into diagnostic criteria, and maybe, into content as to which skin conditions will actually be included. Melissa added that she didn't feel strongly about serious skin injury, but thought the group were all trying to capture the same thing, but haven't agreed on the words to use.

Opting for "severe"

Hervé urged the group to come to a decision, Neil suggested voting in the chat and said "severe" would be acceptable, at least as a start. He stated that he felt like he understood the regulatory perspective, but "severe" seems to be what the group wants moving forward. If there is an asterisk at some point, the group could explain why they chose this approach. Some readers might say it stands for something else, for "serious", but at this point, Neil felt "severe" was the more appropriate and inclusive type of wording.



Report aimed at clinicians, regulators and industry

Hervé concurred with Neil's opinion, saying that it must be made clear in the introduction what is meant by "severe", that the group has considered different options. He asked if the group wanted to vote? Did any members have diverging opinions? This is the time to voice them as, he hoped the group would not come back on this again. Priya agreed, but had a background question about the report as it is not a textbook and is not intended for students who are learning about for the first time. It is also not for people who work in clinical pharmacovigilance centers. So, it is more for clinicians. Is that right? In that case, "severity" is fine. Priya stated she just wanted to confirm the target audience. Hervé suggested that the audience is also regulators, but regulators know when "severe" becomes "serious". The audience is also, not only clinicians, but it is definitely not produced with students in mind. So, Priya summed it up by saying it is not a textbook, but rather, a handbook.

Hervé asked if the group was in agreement. Lesley said it was fine, as long as the rationale is clearly explained. Hervé then suggested the group move on to the discussion about the TOC and gave the floor to Melissa and Neil.

Discussion of merged TOC

Melissa stated that the two TOCs were actually quite similar so merging them was not too difficult. Neil and she fleshed out chapter one, with the different sections it should comprise. This structure is repeated for each of what would be considered severe disease. AGEP and GFBDE were included, as was overlap syndrome which was also raised in the discussions.

- Chapter two

In chapter two, most of the topics had been agreed by the group and Melissa and Neil consolidated them. Melissa said the issue was how to identify what a case is, which is where some of the discussion earlier in today's meeting went into is how can the group come up with a case definition, e.g. Brighton criteria? Or is it going to be more clinically-based. And Melissa stated further that this is where the expertise on the ground is going to be very helpful. Because she didn't think that there's necessarily agreement even amongst all the clinicians about how to define these things.

This is also where we describe severity scales. So one can speak to what has been used in research or in academics, the role of body surface area because that does play into how the Common Technology Criteria for Adverse Events (CTCAE) scale is used. For section 2.4, a table is provided to capture the highlights for each disease and important differential diagnoses. Some are already included, but they can be expanded if needed. Next is the section on "Causality". Seeing that it's a separate step, attributing the etiology to a particular drug is talked about more in this chapter. It includes the different types of assessment tools that are used, the importance of the timeline and drug exposure to the specific DISS and then, the pieces that would help to confirm that the culprit drug is the one causing the reaction.

- Chapter three

This chapter deals more with post-marketing surveillance, so speaks more to a regulatory audience and provides the challenges that are specific to the post-market arena. "Seriousness" can be mentioned here, having previously defined it in the introduction. And this is where the report will describe the different registries, what a spontaneous reporting database is, epidemiologic



assessments, and then special populations. Melissa believed group two had more on this in their table of contents, like HIV and oncology patients. Then, the role of genetic markers within the post-marketing context and how they can be used.

- Chapter four

New skin safety biomarkers. So this is the “up and coming” topic, of what we can do in this field and hopefully predict who will get reactions, and how to then implement that into risk mitigation.

- Chapter five

This section is more focused on the clinician. This was an opportunity to include more clinical care guidelines. And also touched on targeted therapies/biologics and their role.

- Chapter six

It covers mostly risk mitigation and communication.

Melissa asked Neil if he had anything to add. He didn't. Hervé raised two questions: he was not comfortable with the first two chapters because one is included in two. And the TOC the talks about “serious” which has been mentioned before and then the TOC describes a broader aspect of what Melissa referred to as “detection”, identifying the case. So, Hervé believed everything could be put in the same chapter. His second point was, when working on the DILI report, there were interesting discussions about how to detect and identify this type of reaction during a clinical trial, but there is no mention of that in this TOC. Is it less important when it relates to the skin vs the liver? These are my only questions. Other than that, Hervé fully agreed with the TOC. So, maybe we can see if chapters one and two can be merged together and if a specific chapter on clinical trials should be added.

[Experience on data monitoring committees/“mask-ne”](#)

Neil intervened to say he can comment on the clinical trials question as he is on a fair number of data monitoring committees. Because there has been a history of some kind of rash during early development, but wanted to monitor that as part of their ongoing evaluation of the drug being studied. There are some things that are specific to that. The latest issue Neil has seen is a lot of patients who have had acne related to masks have what is called “mask-ne”. But companies get nervous and don't know that other companies are experiencing the same issue. That is a shame. Everybody is dealing with this in their own way, but Neil isn't sure if there was something in particular that needs attention? Hervé responded that of course, it is difficult to say what an effect is related to. It has to do with the power of the causality assessment. So, is a different approach needed when one realizes that there is no clear causality assessment? Or, can one consider that a clear definition of what could arise is enough?

Neil responded that this issue has come up several times in the context of data monitoring committees for trials that are already in operation and are moving into a new phase two b or three a and are having a lot of trouble because they haven't used a structured approach. It's the same approach: what's the diagnosis? What's the causality?



Is there a need for more information to define a case?

Hervé interjected to ask if one doesn't need more information to define the case or make an assessment. As a pathologist, one needs much more information in the pre marketing authorization phase than after, when one knows exactly where one wants to go. So when it comes to the report, does one need more information in the clinical phase?

Neil didn't think this was necessary. There was no "HY's" rule or blood measures like Liver Function Tests (LFT), etc... It's "what's the rash?" And what do you think the causality is? There is a strict approach to that using Bayesian inference. It's something that can be solved, but it's quite different from the liver. Hervé agreed and asked the group if they had any comments.

Alex agreed with Hervé because in the post-marketing space, one looks at the aggregate data and the terms, e.g. gender, demographics, etc... Whereas in pre-marketing, we have the opportunity to collect more data at more granular level, in the labs, etc... So, he wondered if some guidance could be provided, e.g. a kind of ECRF (Electronic Case Report Form) or a standardized narrative in the pre-marketing space to guide the clinicians in collecting data.

Neil thanked Alex, saying it was an interesting point. So let's say a patient is a subject in a clinical trial and needs a definition of DRESS. Hepatitis is clearly one of the major systemic side effects. So then you're looking at, you're looking at a DILI in a DISSI. Under those circumstances, Neil wondered if people who are seeing these reactions need to do a more comprehensive assessment as they are already quite comprehensive. There are literally thousands of pages of data in the tables one gets. So, Neil was not sure there was anything to add other than "make a diagnosis and then look at the causality". Lumping is important too.

It bothered Neil early in his career was that patients with DRESS, one patient would have a fever, a rash and hepatitis, another has a fever, rash and meningitis. Yet another has fever and rash, but they would each be individual diseases. And if you have eight of those, you have eight people with the same disease. It's not eight different diseases. So, he felt maybe this could be described as part of the issues the group will describe in the report and include it in the structure. He asked if someone had a suggestion about what should be done on this. Hervé offered that at a minimum, the approach could be to have two different templates of what is a nice DSL (?). This following criteria could be of interest when it comes to the further assessment of the cases. Or, does one consider that ultimately, the criteria that will be used are enough? So, it could be two different templates of collecting information and adding an extra point for clinical trials.

A lot of data, but poorly presented

Melissa commented that like Neil, the assessment of the disease and causality is the same no matter what stage you're in. But she agreed, it could be helpful for those in the development phase, to understand how rare it is to find these types of adverse events. And in her experience in reviewing cases in the drug development phase, often, there is so much data, but it is not presented well to make their case. Maybe that's where the group could provide advice and guidelines. She didn't believe the group needed two different templates because the data points were similar, but they would be able to provide much more information in the drug development space.

In reviewing cases, the piece that Melissa tries to recreate is the profile of drug exposure with the onset of symptoms. So maybe that is the advice that would be helpful to those in industry and drug



development, to better flesh out their cases, because she has seen different programs do it differently, like some will get five different dermatologists on board and review all their cases and submit letters, you know, in support of what the AE is, and others just data dump, and we get all these tables, which then she has to create the graphical profile.

Assessing risk in a clinical trial

If it helps drug development, the report could explain these steps and how it can be integrated into their signal detection and their programs. That might be a good point. It's a big issue, Neil said. He added that several of the ones he's been involved with lately, want him to give them a quantitative assessment of the risk, maybe even in gender differences, except the data is blinded. It makes no sense. When Neil is on a Data Monitoring Committee, he can see in the unblinded session, but not in the blinded session. And besides, it can pollute the information if there are several trials and people are stating the number of rashes or DISI events, and maybe half of them were on placebo.

To Alex, both marketing and pre marketing are different in the sense that pre marketing is more about data collection. And post marketing is more about data interpretation. So in terms of data collection, if we can get some guidance on what kind of data we should be collecting, or what kind of data we should be aggregating to better understand the skin reaction, is going to be very helpful. Whereas post-marketing is more about signal detection, e.g. running a certain kind of filter on the post marketing data and see what one comes up with.

What is expected of industry drug developers?

Ariel agreed with Alex's point of view. In clinical trials, one has the luxury of structuring the ECRF, for example, and have tools at our disposal to obtain information. So as with Neil's experience on DMCs, that's something that industry would like to have. What are the parameters that are required when one is evaluating a case? Ariel said this information is known, but it would nevertheless be good for the group to provide this guidance based on Neil's experience and Melissa, what do they expect from industry?

According to Melissa, this was challenging just because rash is so common, and when she sees the data and all it says is "rash, rash, maculopapular, pustular rash" how can she make sense of this?

Photos

On the one hand, Melissa wonders how hard it is to take pictures of this, but realizes, at the same time, the large number of patients who are enrolled. So, maybe it would be helpful to provide guidance of when it is reasonable for a drug development program to institute another layer of like, I don't know what you want to call it "Derm"-specific data collection? Or, a cut-off by surface area, but even this is hard because one could have maculopapular eruption over 100%, but it might not be severe, because it's just on the skin and no fever as Neil mentioned earlier. So, maybe a kind of Venn diagram would be helpful. If you have this constellation and maybe further evaluate those cases and provide more data points. Ariel concurred by saying that those things would be helpful, e.g. photos. He mentioned the agencies asked for photos because a narrative will be different for every applicant. So, things like this that can be recommended and included in the evidence to be presented to the DMCs or regulatory authorities, would be extremely helpful.

Neil agreed with Ariel's points, but suggested that photos are not a simple thing. And depending on the lighting, the condition could appear differently and lead to different diagnoses. So, photos can



be useful, but the check forums where people check off maculopapular, Neil suggested, were not helpful at all. He has just evaluated a large number of those from an international study. Comments such as “it looks dramatic in one area”, but it “looks nodular in another area”. So is it Prurigo Nodularis? Is it with dermatitis? Or does it really mean anything and you've got non experts giving you basically non data. So, you have to be careful with photos. They can help but... Pathology is just as useless because it is basically going to show inflammatory changes. It won't necessarily give you a big diagnosis.

Ariel concurred, saying this was important. He understands that pathology might always be helpful, but sometimes one needs a pathology result in order to define the condition, e.g. SJS. Having that confirmatory evidence that can be presented. Is a biopsy or the pathology necessary? If regulatory authorities instruct applicants to obtain it (and photos too), they will find a way to do so. Just to rule out the incidence of DISSI or not - that signal- it would be beneficial for industry to know when you've had a signal, how to properly document it.

Data that is as objective as possible

To Violeta, from a development perspective, it would be useful to come up with items in the CRF that are as objective as possible and as mentioned previously, photos might not be the easiest way to proceed. So, if we can get data that is as objective as possible. So for instance, presence of facial edema, extent of the rash and not go to the specific characterization of the skin lesions because this is subjective. Lab parameters, so AST, ALT, eosinophilia presence or not, atypical lymphocytes, to be as objective as possible. That would be one proposal. Extent of the rash could be subjective, but it's more objective than the description of the lesions.

Hervé asked if there were any other comments. Priya came back on an earlier point and asked for clarification as to whether case descriptions could be used as diagnostic tools for clinicians only or could they also help assessors either at NIH or regulatory authorities to classify or identify cases. Is it case definitions for pharmacovigilance experts or only for clinicians. If given the choice and if it's feasible, Priya would like to see that it is aimed at both audiences.

Case descriptions

Hervé stated it was an important point because most assessors are not specialists. And that the group needed a more simplified approach. His experience as a member of EMA/PRAC is that the discussion focused more on microdata. Several times, I tried to ask about the cases, but was told that it was not the right place to do that. So he agreed that it was important, but wasn't sure this issue is relevant for regulators, but as he isn't a regulator and was therefore, open to any comments.

Based on Priya's earlier comments, Melissa stated that case definitions are important. In the drug development phase, what you're really worried about is what if it could be a DISI? So, those criteria, would be different to set your alarm off compared to post-marketing, where, one would want to know if it's a DISI. So, the criteria are going to be more strict because one is dealing with less not that the quality is poor, but less details whereby one doesn't get to see the whole picture and it's already been filtered through many layers. One suggestion is for the chapters to address both because it is different. What the signal is going to be will be defined differently if one doesn't know the safety profile of the drug versus when one has more information post-marketing.



And actually, what comes to mind is for scleroderma, the EULAR ACR criteria classification criteria are highly sensitive, which is useful. If one applies this criteria, then you probably have the diagnosis and that means more in post marketing than maybe in the pre market drug development phase if one is talking about a DISI comparison.

Helping pre and post-marketing

Lesley felt it was important to help both pre marketing and post marketing situations because for her case assessment, it is very relevant to have some kind of, what the group had for SCARS for example, where it is relevant to have a reference for what the diagnosis is going to be and to have some harmonization for how things are done for a product in development. So, one can assess the safety profile.

Coming back on Priya's question, Hervé asked what would be the ideal world for her? (Priya had left the call to join another meeting and would come back in 30 minutes). Hervé continued to say, there was a need to have something different when it comes to pre-marketing authorization. He asked Melissa and Chia-Yu if they would agree to working on a smaller template and see how this evolves in the discussion, if there is a need to go into more detail or not.

Chia-Yu agreed with this approach, saying that the approach to DISI is quite similar, but the skin is a visible organ. So usually we approach this piece with the same approach as the tools are the same. Whereas, it is quite different with DILI during the pre- and post-marketing phases. He agreed, the group could use the current table to complete most of the approaches and work for DISI.

Melissa agreed, saying it is useful to have both and in terms of the table of contents, we can move that as either a separate chapter, the preclinical part or pre marketing part.

Merging chapters one and two

So, Hervé confirmed there was agreement on the two different approaches, but even if they are quite similar as you say they are very different. So this is this was the first issue. Of course, there is many more. He asked about merging the first two chapters as there were redundancies and opened the discussion up to the group. Melissa said she isn't against it, but was more concerned about the length of the chapter. Alex intervened, saying maybe just simply changing the order where you start at the highest level, and then you take a deeper dive into individual conditions. Now, you agree that we should start with chapter two and to go even further, to put chapter one into chapter two and at least, change the order.

Summarizing changes to the TOC, Hervé outlined the following:

- Agree on a definition of severe vs serious
- Adopt a slightly different approach when it comes to pre-marketing authorization and post-marketing authorization data collection.
- Promote current Chapter 2 to become the first chapter and then the current Chapter 1 becomes the new Chapter 2.

He asked the group if there were any further comments on the proposed merged TOC?

There were none so, he broached the subject of how to split the group up and say who does what. Alex had one last point and asked if the group was going to address the issue of new modalities, new



therapeutic modalities? Like checkpoint inhibitors. Is skin injury any different with these new modalities?

Targeted therapies

Any comments from dermatologist colleagues? Melissa intervened to say that she and Neil had put in one of the chapters a section on targeted therapy, but Neil and she thought it was up to the group how much we want to go into that piece. Melissa said, she thought it would be useful, on the regulatory side in any case and would like to see it included somewhere.

Neil suggested that although it would evolve, what's important is not just the anti-inflammatory piece, but in cancer therapies, the drug is keeping the patient alive and if they are having an adverse event, one has to try to deal with it. But you can't just stop the drug, because the patient will die. So, in Neil's experience, these drugs are a real game changer, both on the approach and other aspects. If the person's getting cancer therapy that is causing a rash and it's the only therapy or combination therapy that works, it also opens the door to many other issues related to other types of drugs that are going to be causing rashes and different mechanisms and there are so many that are coming out, it's mind-boggling. Neil stated one couldn't cover all of that in just one chapter.

Alex asked Neil if the concept of benefit risk was actually embedded into each of the sections. Neil responded that normally, one would want to stop the drug. If it's a situation in which you can't stop the drug, then you have to look at the risk/benefit, or more accurately stated as harm:benefit. He said, this point could be included in the report.

He said, he felt it was already covered to some extent and asked Melissa for her thoughts. It's the chapters six point 7.1, actually, so that'd be 6.1. As Priya commented in the 2nd meeting in April, risk communication and mitigation should be included throughout development and post-marketing and in the drug development space, one would approach it differently. Melissa recounted experiences with colleagues where there is an oncology patient and the dermatologist wants to be involved earlier because they can help determine if the treatment can be continued or not. And that might be advice one would give for clinical trials. So that way you can collect the data and help the patient, the best that you can.

With some of the early therapies, it was common to see patients with horrible rashes and they were worried they would have to stop their cancer drug and all it was doing was clearing up their actinic keratosis and you would say, this is good news, but they don't believe you when you say they will get better. So, there are different stories there, just like clinical trials, it's a different story when you start doing targeted therapies

Dedicated section on epidemiological studies?

Violeta suggested that for oncology patients, could the group also include in chapter five, special populations of interest? That was the original idea. Hervé asked Alex if he was comfortable with this. Alex replied that he was. Hervé then asked if there were further comments on the structure of the table of contents? Any questions that people would like to raise? Priya asked why there should be a specific chapter on epidemiological studies by itself. Is that something the group should consider. The other observation was that she found the chapters on clinical and regulatory quite different whereas the purpose is to bring the two worlds together. She was worried about this as the intent is to show how the clinical world can do patient safety, but can also inform regulators and how



regulators can help the clinical world for patient safety. So to bring that better together, like in the chapter, which is currently chapter three where it says causality assessment at individual level. Could we also have the idea about the outcome assessment when the spontaneous reporting kicks in and bring that together. So, it's not only about the causality assessment at individual level and if we then have a chapter on post-market authorization safety studies, for example, we could put the causality assessment at population level if that's relevant to this specific technical pictures. Maybe it could be inserted here.

Hervé asked Priya what she would propose. She replied that from a pragmatic point of view, it would have to be in chapter two and add the outcome assessment in the chapter on causality assessment and explain that then, something qualifies for spontaneous reporting.

[Inserting outcome assessment in the chapter on causality assessment at individual level](#)

Hervé asked Priya what she meant by outcome assessment. She replied that it was the discussion we had in the beginning, with the specific outcome, the spontaneous reporting becomes relevant for the clinician. If we don't write that in the chapter they would read, because they are interested in causality assessment at individual level, then we lose that because if we have a separate chapter on regulation, which a clinician would not necessarily read. A clinician would not necessarily read the regulatory chapter. So I have to help them become aware, or now the spontaneous reporting kicks in as an action for me as a clinician, and that's why I would put that into that chapter.

Melissa supported Priya's point of view. Saying that she gives talks on pharmacovigilance to healthcare providers and tries to connect with them on their duty and ethical responsibility to submit reports when they see potentially serious reactions. As a healthcare provider, for post-marketing, one has the duty to patients to report cases even if it takes a little extra time. It is part of managing a patient to report a case to the regulatory authorities if it's a potentially new safety signal. And this is for those with a serious outcome. So, that's where the outcome assessment comes in. She asked Priya if she agreed with that. Priya said yes. Hervé then asked Priya if she could provide more details, e.g. What would be the title of the chapter to be included in Chapter two? And where would it be inserted?

Priya suggested it could be included in Chapter 2.5 "Assessing outcomes and reportability". Melissa added that she likes "when to report when it's serious, such as if it's a new drug within three to five years of marketing authorization and it's not currently labeled: these are the topics Melissa tries to communicate to healthcare providers. Hervé asked if the group agreed with this and asked Priya to send an email with her suggested changes to the TOC. Regarding her request for epidemiological data, Hervé said he assumed it would be in the introduction. He asked if there were any other comments on the TOC? No.

[Next steps: assigning WG members to TOC chapters](#)

He put it to Chia-Yu and Melissa to decide how to divvy up the work and how to split the group into two subgroups and who will join which group? Melissa said she assumed it would be divided by chapter as they did for the DILI report. People could self-nominate to join a specific chapter to read and write that chapter. Chia-Yu supported this idea to break it down by chapter. Melissa will contact Catherine with a proposal for how members will be assigned to the different chapters.