



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

**Day1**  
**2 February 2021 Meeting**

### Meeting Minutes

#### Participants

Susan Atkinson (Novartis), David Brott (Takeda), Siew Eng Choon (Monash University), Chia-Yu Chu (National Taiwan University Hospital), Roni P. Dodiuk-Gad (Emek Medical Center), Leslie Dondey-Nouvel (Sanofi), Koji Hashimoto (Ehime Prefectural University of Health Science), Alexandre Kiazand (AstraZeneca), Haur Yueh Lee (Singapore General Hospital), Sylvia Lesperance (Novartis), Hervé le Louët (CIOMS), Filippa Nyberg (Karolinska University Hospital), Ariel R. Porcalla (AbbVie), Kateriina Rannula (CIOMS), Lembit Rägo (CIOMS), Violeta Regnier Galvao (Eli Lilly), Melissa Reyes (US FDA), Sarah Schlieff (Bayer), Neil Shear (University of Toronto), Sabine Straus (MEB), Takahiro Ueda (Office of Pharmaceutical Safety I, PMDA).

#### Regrets

Matt Doogue (IUPHAR/University of Otaga/Christchurch), Gerd Kullak-Ublick (Novartis).

#### Introduction

- Lembit Rägo, Secretary General, CIOMS, welcomed the new CIOMS Working Group (WG) on Severe Cutaneous Adverse Reactions of Drugs (SCARs) members.
- He continued by briefly introducing CIOMS working groups and CIOMS in general.
- Hervé le Louët, President, CIOMS, welcomed the new WG members, with special thanks to everyone for sparing their time during the Covid-19 pandemic and chaired the meeting.
- Kateriina was rapporteur at the meeting.

#### Discussion

- Hervé opened the discussion by explaining that the idea to create the WG derived from a collaboration with a colleague from the National Taiwan University Hospital and working with the register for severe cutaneous reactions. The idea developed further when working in the Pharmacovigilance Risk Assessment Committee (PRAC) in the European Medicine Agency, where a need for a more explicit definition of SCARs and its management became evident.
- The goal of the guideline would be to summarize the existing information on the three main SCARs: the Stevens-Johnson syndrome (SJS), the Lyell's syndrome and the acute generalized



exanthematous pustulosis (AGEP), but also concentrate on other reactions associated with drug intake and new biological drugs.

- Hervé suggested dividing the WG into two subgroups: the first subgroup would describe what is known on Lyell's syndrome, SJS and AGEP and the second subgroup would focus on other drugs, which cause cutaneous reactions. As each drug may lead to a cutaneous reaction, it is essential to choose the drug of interest and the reaction of interest.
- He concluded that the meeting's goal is to identify the target audience of the outline and suggested focusing on the regulatory agencies, health care professionals, academia, and industry.
- It was agreed to limit the WG meeting to one day and continue by:
  - a roundtable for the members to introduce themselves;
  - a discussion to agree on the target audiences of the guideline;
  - creating two subgroups to work independently from each other and prepare for the next meeting in the upcoming months.
- Responding to Lembit's request, Hervé added that as he has been appointed the CEO of Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring, he has the possibility of accessing the vast database, which would be beneficial in designing the future work of the WG.
- "Tour de table" followed for all to introduce themselves.
- Lembit explained a few practical matters about the CIOMS WGs in general:
  - Each CIOMS group finalizes a guideline, which will be both in electronic format and printed. All CIOMS reports are free to be downloaded from the CIOMS website.
  - The draft minutes from meetings will always be provided to the members to review and approve.
  - Where WG members consent to meetings being recorded for the purposes for taking minutes, the recordings will not be used for any other purpose and will be deleted as soon as possible.
  - The CIOMS Secretariat will provide a support staff member to the WG to act as a primary contact, who will help with setting up Zoom meetings, writing minutes, and who will assist with general communications.
  - Each WG has its own section on the CIOMS website where the WG documents are available. Some content is open to the public e.g. the Concept Note and minutes, and other content is available only to the WG members behind password-protection e.g. working documents and publications of outstanding importance shared among the WG members.

### **The target audience of the guideline**

- Lembit suggested all WG members share their opinions on the target audience of the guideline, reiterating Herve's suggestion that the document would be beneficial to regulatory agencies, clinicians, academics, and industry involved in product development.
- Hervé added patients as an important party in the process, and Lembit agreed that having a patient representative in the WG would be valuable, and the matter should be discussed at a later date.



- Sabine commented that overall interest in the topic exists among regulators, assessors, representatives of the pharmaceutical industry and patients worldwide as it is a severe adverse drug reaction (ADR).
- Chia-Yu added that there is a need for a more clinical phenotype-based approach for the definition of each phenotype. As there are several dermatologists in the WG, each specific topic can be approached.
- Siew added that with patients being the target audience as well, and as the goal of the WG would be to define the phenotype and based on the phenotype the causality, compiling a layman summary of the final report for the patients would be more helpful.
- Hervé commented that it is common to discuss SCARs in terms of genotypes, but it would be more beneficial to interpret genotypes in relation to phenotypes.
- Neil added drawing from his experience that a different mindset exists in the field of oncology, which would perhaps require another subgroup to tackle the issue regarding the adverse reactions, targeted therapies, and new emerging therapies in oncological treatment.
- Hervé summarized the discussion identifying four target audiences: industry personnel, regulatory agencies, health professionals (including academics), and patients.
- Alexandre commented that in order to include academics, certain aspects that are specifically relevant to academics, e.g. genotype, would have to be examined more thoroughly.
- Leslie added that within the industry, the target audience includes several departments, e.g. clinical departments, pharmacovigilance and risk management departments. It is essential to ensure alignment of the language with different target audiences.
- Ariel commented that the guideline would also be beneficial for other paramedical professionals, e.g. epidemiologists or researchers, not necessarily clinicians.
- Hervé agreed and commented that similar information should be conveyed to regulatory agencies, and the focus should also be on the representatives of the agencies not familiar with the clinical effect of SCARs.
- Phillipa added that having read the Organisation for Economic Co-operation and Development (OECD) report on economic aspects of patient safety, in terms of target groups and language, it would be beneficial to also be visible in that context.
- Hervé agreed that the new angle must be considered.
- Lembit concluded that although the discussions on target audiences could be fine-tuned and adapted during the future meetings, the WG members have reached a consensus and proposed continuing with the second discussion point.

### **Framing the work**

- Hervé introduced the second discussion point by suggesting forming two subgroups inside the WG, where the first subgroup would tackle the topic of significant SCARs for which there are several guidelines available and the second subgroup tackle the types of reaction and the types of drugs.
- Chia-Yu agreed that the WG should divide itself into different groups. A group dealing with SCARs would be essential, including SJS, toxic epidermal necrolysis (TEN) or DRESS, AGEP, and generalized bullous fixed drug eruptions (GBFDE). IgE-dependent anaphylaxis types form another group of severe reactions. Some novel targeted therapies for cancers and other



biologics for immunologic diseases must be included. The first division of the WG should be based on the phenotype approach and the second on therapeutic category approach.

- Neil commented that when phase one studies are discontinued, or if a severe adverse event, e.g. SCAR occurs, and the data is not collected, the information on using certain chemical structures and genetics is lost together with the learning opportunity, thus creating possible repetitive mistakes.
- Hervé commented that if two types of groups are to be formed and the first would be discussing major SCARs and the second other phenotypes of reaction, it would be easier to proceed by phenotype, and decide if there is any overlapping with biologics. If not, every group would then approach different chemical, anticancer and biological drugs.
- Filippa commented that the suggestion about using phenotypes is feasible and practical. She continued by mentioning drug-induced subacute cutaneous lupus, which is caused by many drugs, characterized by a long diagnosis and causes similar reactions in many patients.
- Alexandre asked whether the WG will focus on SCARs or drug-induced skin reactions, and added that both are extremely important, at least for the industry.
- He elaborated that the focus of the WG must be agreed upon considering that SCARs is relatively rare but has a significant impact on drug development. There is also a demand to describe drug-induced skin injury (DISI) in general, as there are many misdiagnoses on DISI, which may not be as important as SCARs but is still significant.
- Hervé added that the discussion regarding the focus of the guideline would have to be launched even if the decision will be made later and suggested WG members to offer their opinions.
- Siew commented that adverse drug reactions are widespread and most of them are maculopapular eruptions. She suggested to concentrate on SCARs and divide them into different phenotypes. One subgroup would investigate the best way to define different phenotypes or SCARs, which are potentially life-threatening, and the second subgroup would investigate drugs causing the different SCARs phenotype. In case of oncology drugs, the SCARs are quite different, and perhaps there should be a subgroup dealing with oncology-induced types of DISI.
- Ariel agreed with focusing on SCARs since the outcome of SCARs could be life-threatening. Although it is rare, the fact that it occurs in association with a drug could also impact the drug labelling quite significantly. Diagnoses guidelines would also be beneficial in terms of pharmacovigilance and from the regulatory perspective as well.
- Melissa commented that the guideline would help create alignment in communications between the industry, regulators, and other parties. She added that her interest in SCARs lies in the correct diagnosis and assessment of risk and how to effectively convey it to the healthcare providers and patients.
- She added that focusing on SCARs is important, as is creating case definitions and diagnoses that could be shared with partners with guidelines on how they would be able to collect that data.
- Sabine agreed that practicable definitions and how to assess them based on spontaneous data or data from clinical trials would be useful for the regulatory agencies.
- Hervé asked whether it would be possible to circulate the draft EMA guidelines on the mentioned topics and Sabine agreed to check.



- Hervé summarized that there is a consensus regarding SCARs and proposed to consider Filippa's suggestion to discuss the issue of biologics and vaccines further.
- He added that the WG's goal is to include the basic information but to use the opportunity to explore new concepts as well.
- Lembit commented that considering the present situation, there might be some added value in including the topic of biologics and vaccines. If necessary, additional members with expertise on the specific field can be invited to join the WG.
- Haur Yueh commented that SCARs should be the main focus of the guideline, but as biologic therapy and immunotherapy remain outside the classical phenotype, these important groups should not be left out.
- Melissa agreed and added that with SCARs, there is a phenotype that is possible to describe. From the regulator's perspective, it is essential to have the information on a label presented in a uniform language. From a dermatologist's perspective, patients do not always fit into the descriptions reiterated in the textbooks. There is an opportunity for the WG to collate the existing information and be forward-thinking.
- Neil added that clearer guidelines on the characteristics and appearance of the reactions are needed. Correct diagnosis is the starting point for the discussions.
- Hervé commented that besides being able to determine the correct diagnosis, causality assessment is an important issue.
- Neil agreed that causality assessment is critical for patient safety and the integrity of the WG conclusions. He elaborated on using Bayesian approach in causality assessment as it allows for a rational way of operating and ensuring that both parties are presented with the same data when circulating information.
- Leslie added that the physician's case documentation might create confusion and should be discussed.
- Violeta added that in terms of identification and the clinical manifestations, oncology drugs seem to need a different approach. Considering the type of population, the compound's benefit-risk profile is different. Having a separate evaluation for oncology drugs in the report might be beneficial.
- Hervé inquired whether it would mean discussing the chemotherapy drugs together with the immunology drugs.
- Violeta responded that for oncology patients, the approach might be different, and based on personal experience, the presentation for some immunotherapy agents is different from what is provided in the textbook. More specific management of the topic must be specified but oncology patients might need a separate evaluation.
- Chia-Yu commented that skin reactions due to oncologic treatment do not necessarily need to be discussed as a separate group and proposed to start with the common types of drug eruptions, e.g. maculopapular eruptions, followed by more rare severe adverse reactions. Following that another division into more specific sections could be formed, discussing the new types of oncology treatment. In the specific sections, it would also be possible to start with the common type of eruptions and then a more detailed section could follow.



- Sarah agreed that a causality assessment is of significant importance and emphasized that it would be beneficial to have a common methodological approach across drugs. She added that the specifics of certain oncology drugs might be highlighted in some subsections.
- Filippa commented that many different drugs, including biologic and oncologic drugs, can in certain genetic types induce subacute cutaneous lupus. Adding subacute cutaneous lupus to the discussion would present an opportunity to widen the knowledge in terms of another phenotype typically not included in SCARs group.
- Filippa concluded by offering to send some articles on what has been investigated at Karolinska University on subacute cutaneous lupus.
- Chia-Yu agreed that the specific topic about the oncology treatment or even immunologic treatment or some biologics should be considered separately because they cause different types of eruptions. The same, the more systemic methodology should be used to approach different sections.
- Hervé concluded that even when discussing SCARs, the possibility of a common type of drug eruptions should not be forgotten. It is not necessary to have a detailed description of common drug reactions, but for SCARs, it must be mentioned because they are dangerous, and they will influence the industry.

#### **Subgroups' task**

- Lembit suggested forming two subgroups composed of a balanced number of representatives from academia, industry and regulatory agencies. The two groups have the same task: to define the WG's high-level guidance content (major topics, potential chapters, respective subsections in the chapters, appendixes, etc.). The proposals would then be merged into a single vision on what the content would look like for the whole WG.
- Kateriina will set up virtual subgroup meetings.
- Leslie enquired whether there was a template or an example to consult when writing the Table of Contents.
- Lembit responded that it is possible to circulate an example from another CIOMS WG, but it is for the use of the SCARs WG only and not to be shared with parties outside the WG.
- Hervé added that the discussion points from the current meeting would form the base of the subgroups' work in compiling the draft Table of Contents.
- The WG members agreed to use the next day for the first subgroup meetings.
- Neil enquired about the official title of the WG and Lembit responded that for the moment it is CIOMS Working Group on SCARs, but if there is a need to change it, the subgroups are welcome to suggest a new title to be discussed at the next WG meeting.

#### **Closing remarks**

- Hervé thanked all for joining the meeting and for the beneficial discussions despite the constraints of a digital work environment.
- Lembit thanked the WG members for their dedication at this challenging time, and for the continuous commitment, as all work under difficult circumstances due to Covid-19 pandemic.



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

### Day 2

### 3 February 2021 – Subgroup 1

## Meeting Minutes

### Participants

David Brott (Takeda), Chia-Yu Chu (National Taiwan University Hospital), Leslie Dondey-Novel (Sanofi), Koji Hashimoto (Ehime Prefectural University of Health Science), Alexandre Kiazand (AstraZeneca), Filippa Nyberg (Karolinska University Hospital), Kateriina Rannula (CIOMS), Violeta Regnier Galvao (Eli Lilly), Melissa Reyes (US FDA).

### Regrets

Roni P. Dodiuk-Gad (Emek Medical Center).

### Introduction

- Two subgroups were composed of a balanced number of representatives from academia, industry and regulatory agencies, and presented with the same task: to define the WG's high-level guidance content (major topics, potential chapters, chapter subsections, appendices, etc.). The proposals would then be merged into a single vision for the whole CIOMS WG on SCARs.
- Melissa was appointed as the subgroup's chairperson.
- Kateriina was rapporteur at the meeting.

### Discussion

- The subgroup referred to the CIOMS Drug-Induced Liver Injury (DILI) report Table of Contents for guidance, as the DILI framework seemed applicable to the discussion of the cutaneous adverse reactions.
- The subgroup 1 team questioned whether the focus of the document would be only on SCARs.
- David commented that, as discussed during the whole Working Group (WG) meeting, the main focus would be on SCARs. However, other serious cutaneous adverse events, e.g. drug-induced subacute cutaneous lupus, would also be included.
- Filippa agreed that the WG's main task is to focus on SCARs and added that the inclusion of autoimmune diseases in the report would possibly offer an opportunity to draw practical conclusions in terms of preventing drug-induced subcutaneous reactions.
- It was agreed that more uncommon reactions should be included as well.
- Alexandre asked if the document is to consist of just two chapters: SCAR and Drug-Induced Skin Injury (DISI). If so, DISI could include subsections with all other diagnoses.





- Melissa agreed that this needs to be decided, and added, in reference to the WG's discussion, that drug classes and the consideration of medications' mechanisms of action are also essential.
- David suggested to first outline the essential information and decide at a later stage how to prioritise the contents.
- It was decided to first describe cutaneous adverse events and then continue in more detail with SCAR and non-SCAR.
- Filippa suggested that it would be interesting to include a few sentences on other types of skin reactions, e.g. contact allergy and sunburn.
- Melissa suggested including these reactions in the non-SCAR section of the document.
- It was then discussed whether the reactions would be grouped by their mechanism, and it was decided to group the reactions by Type I, Type II, etc.
- Alexandre suggested to title chapter 1 "What is Drug-Induced Skin Injury," and to include Types I-IV with their definitions in this chapter.
- Melissa added section 1.1. as "Introduction to Skin Injury".
- Leslie suggested adding Section 1.1.1. and titling it "Severity/Seriousness", as there are potential statements on the different severities of skin reactions.
- Leslie enquired whether some information would be needed in the introduction about causality assessment, and it was decided to add it as a separate section.
- Filippa commented on a number of the proposed subgroups possibly by offering the example of a delayed-type or a graft versus the host skin reactions. These reactions do not necessarily belong in the drug development phase but are pathogenetically similar. Filippa enquired as to whether they would be addressed, and if yes, under which subsection.
- Alexandre shared his experience from his work on the DILI report, wherein discussions began with the definition of DILI, and then the team had debated other challenges, e.g. how to tackle causality and how to manage MedDRA to scan the database.
- Violeta added that in terms of the case, evaluation, and causality assessment, the focus should be on SCAR.
- Koji agreed, and suggested to first define SCAR, and then under the non-SCAR subsection, to include biologics or oncology drug-induced severe drug eruptions.
- Alexandre added that certain elements would apply to both the pre- and post-marketing period, e.g. clinical care or biomarkers.
- Melissa commented since Chapter 2 is about the assessment of cases, the necessary components should be discussed, as it would be helpful for the industry to know what the recommendations are and the relevant data that should be collected.
- Leslie added that the report should include all different types of cutaneous disorders. The industry would be interested in information on how to address SCAR and other less frequent reactions.
- Leslie suggested including a subsection, "Differential diagnosis: SCARs vs non-SCARs".
- Koji suggested to add ophthalmology under speciality consultations in section 2.1, titled "Identifying and Characterising DISI in Drug Development" and a list was created, consisting of "allergy, immunology, dermatology, ophthalmology, gynaecology, urology, and other organs".
- Melissa suggested describing non-SCAR cutaneous adverse reactions in more detail in the appendices, as those diagnoses have less concrete information about them.





- Alexandre suggested adding a table, “Differential diagnoses: SCAR versus Non-SCAR” and to insert all necessary elements in the table, e.g. laboratory results, morphology, etc. The headers would be SCAR, non-SCAR, as well as other prominent skin conditions.
- Violet suggested that in terms of identifying SCAR cases, HLA should be mentioned, and it was decided to add HLA under Chapter 4, “New Skin Safety Biomarkers”.
- Koji proposed adding “Patient history” under section 2.1. as a detailed examination of drug intake is significant.
- Melissa agreed, and suggested adding graphical timelines to the document as it would help in the confirmation of a diagnosis or a causative agent, and the team agreed.
- Melissa added, referring to the "Case report form for hepatic event" in the DILI report, that a similar form should be created for the description of skin injury as well. It would be beneficial for reviewers to be able to determine whether the reaction is more serious, e.g. SCAR, and consider the data points which need to be assessed, e.g. skin biopsy, etc.
- Violet commented that some of the questions in the form could be extracted from the RegiSCAR, and the scoring system might help to contribute. The team agreed.
- Melissa added that the National Institutes of Health working group with representatives from academia, regulators and researchers had created their version of a SCAR case report form. She proposed to share the document as a starting point for the discussions.
- Koji suggested adding a drug-induced lymphocyte stimulation test (DLST) to the document, emphasizing the importance of timing.
- The team agreed to add DLST under Chapter 4, “New Skin Safety Biomarkers”.
- In reference to the first section of the Table of Contents draft, Melissa raised the question of the representation of a non-SCAR section of the document.
- Chia-Yu recommended for a more systemic review to briefly introduce the Type I, Type II, Type III, and Type IV hypersensitivity reactions, which were then added as section 1.1.2. Hypersensitivity Types.
- Melissa commented that in the SCAR versus non-SCAR section, maculopapular eruptions, wheals, and angioedema are phenotype reaction patterns, whereas, in the case of fixed drug reactions, there is a specific diagnosis creating a challenge in organizing the topics into respective sections in the document.
- Chia-Yu suggested that anaphylaxis, under Type I hypersensitivity reactions, should be mentioned briefly in the same section with wheals and angioedema, as it is the most severe Type I hypersensitivity.
- The team agreed to add Section 1.3.1. “Phenotypes (bring in hypersensitivity type of reaction): (Reaction Patterns: maculopapular eruptions, wheals, angioedema, fixed drug eruptions, etc.) versus name of hypersensitivity (e.g. subacute cutaneous lupus erythematosus, drug-induced vasculitis, allergic contact dermatitis)”. The team agreed to address the contents and organisation of the topics at a later stage.
- Alexandre commented on the WG’s title, and after some discussion, a new title was suggested: SCAR and other Drug-Induced Skin Injury Working Group. It was agreed that SCARs would remain the focus of the report but mentioning other drug-induced skin injuries is also important.
- Alexandre suggested to include the differential diagnosis table under section 2.2 “DISI case evaluation and minimum required data in clinical trials”.
- Chia-Yu suggested adding the ALDEN and Naranjo score to section 2.3. “Causality Assessment”.
- Melissa commented that in post-marketing surveillance, since there are spontaneous reports, not enough data is collected to be able to use the ALDEN or Naranjo score. It is different for



researchers and clinicians, as they have more access to the data, and that is where the case narrative or the case report form would serve useful to obtain all data.

- Melissa added that if the case report form would be available, the information would be included in spontaneous reports and medical literature.
- Koji suggested adding a patch test to section 2.3. and Chia-Yu agreed that the skin tests, including the skin prick test, should be included.
- It was agreed to add MedDRA under Chapter 5, “Post-Marketing Surveillance for DISI or SCAR”.
- Melissa referred to the difficulty in assessing skin reactions on individuals with a pre-existing medical condition, particularly in skin disease, thus “Concomitant medications, background skin diseases, and other medical conditions (e.g., HIV, EBV infection, oncology patients)” was added to Section 2.1 “Identifying and Characterizing DISI” as well as to section 2.3. “Causality Assessment”.
- Alexandre raised the concept of benefit-risk, and it was added into Chapter 7, “DISI Risk Management and Communication”.
- Chapter 3 was deleted due to the overlap with other chapters. Chapter 2’s heading was changed into “Assessing DISI Cases”.
- Melissa commented that in the DILI report, there is a separate section for clinical trials.
- Alexandre added that the reason or clinical trials being separated from post-marketing was that there are more laboratories involved in clinical trials. In post-marketing, there are more clinical symptoms, whereas DISI is mainly clinical. It should be decided whether that distinction is still applicable in the case of DISI.
- Chia-Yu commented that the difference is not that substantial. Leslie added that the difference with the development is the level of information obtained. More information can be obtained in clinical development on concomitant medications, and more experts on the skin are expected to be involved.
- Leslie suggested the addition of a specific subsection on the specificities of drug development.
- Melissa suggested creating sections 2.4, “Considerations for Drug Development Programs”, and 2.5, “Considerations for Post-marketing Surveillance” and the team agreed.
- It was then agreed to add an introductory statement under Chapter 2: “Quality and quantity of data obtained during the pre-market phase may be more detailed but is also relevant and useful for the post-marketing surveillance”.
- The team agreed not to have a specific chapter on drug development.
- The subgroup 1 team concluded by agreeing to meet again to finalize the draft Table of Contents before another entire WG meeting.



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

**Day 2**  
**3 February 2021 – Subgroup 2**

### Meeting Minutes

#### Participants

Susan Atkinson (Novartis), Siew Eng Choon (Monash University), Sue le Roux (CIOMS), Sylvie Lesperance (Novartis), Ariel Porcalla (AbbVie), Sarah Schlieff (Bayer), Neil Shear (University of Toronto), Takahiro Ueda (PMDA, Japan), Lee Haur Yueh (Singapore General Hospital).

#### Regrets

Matt Doogue (IUPHAR/University of Otaga/Christchurch), Gerd Kullak-Ublick (Novartis), Sabine Straus (MEB).

#### Introduction

- Two subgroups were composed of a balanced number of representatives from academia, industry and regulatory agencies, and presented with the same task: to define the WG's high-level guidance content (major topics, potential chapters, chapter subsections, appendices, etc.). The proposals would then be merged into a single vision for the whole CIOMS WG on SCARs.
- Neil was appointed as the subgroup's chairperson.
- Sue was rapporteur at the meeting.

#### Discussion

- The subgroup reviewed the draft Concept Note on SCARs and then referred to the CIOMS DILI report as a guide for structuring a draft Table of Contents for the future SCARs report, noting that the skin is a much more complicated organ.
- Neil suggested that "drugs" in the title could be replaced by "therapeutics", although after discussion, the subgroup agreed that the Concept Note title was not necessarily the title of the report.
- Sylvie suggested naming an early section "SCARS phenotypes".
- Ariel added that the report could first name all the phenotypes (definitions), and after that, deal with the issues.
- Siew said that following the previous day's discussion, there should be a general introduction about skin adverse reactions (ADRs), followed by reactions to biologic and oncologic drugs. Each phenotype should start with a definition, and then talk about causality and common drugs for each SCAR.
- Susan brought the Table of Contents from CIOMS DILI report as an example to consider.
- Sylvie said that SCARS would have an additional area of targeted manifestations of biologics and oncology drugs.



- Ariel suggested starting with a typical range of manifestation of skin ADRs, then providing overall rates, and lastly honing in to SCARs frequency rates, hospitalisation rates, etc.
- Siew suggested putting these perhaps into the second chapter, as e.g. biomarkers will have to come under different SCARs. Other topics like clinical care and risk management also need to be added.
- Susan said the introduction should include the aim of this document, such as addressing some of the gaps.
- Siew said the report has to address problems with causality and ADRs on new targeted therapies.
- Lee added that while clinical issues are a lot easier to define, this would be a good platform to address some of needs and issues from the regulatory and the pharmaceutical areas not typically covered in other statements on Stevens-Johnson syndrome (SJS).
- Neil agreed adding that diagnosis complexities should also be addressed as well as the suffering that patients go through, e.g. after toxic epidermal necrolysis (TEN).
- Sylvie raised the issue of additives, excipients - where do they play into it?
- Susan suggested having a generic approach and special scenarios situations e.g. oncology.
- Ariel raised the idea of having benefit-risk profile assessment for each oncology patient (but different for immunology drugs).
- Sarah said this comes under risk-management.
- Sylvie asked about including tele-dermatology and remote diagnoses.
- Neil thought not because diagnoses was very important to get right and most artificial intelligence is looking at melanoma, and therefore he thought it was inadvisable.
- Sylvie suggested parking the idea for now.
- Ariel raised the subject of identifying data from clinical and non-clinical sources and providing data to industry.
- Neil added that under Assessing SCAR Risk he worries about CIOMS I reports, for example, were they seen by a dermatologist? Follow up notes on CIOMS reports are helpful.
- Siew added that under Clinical Care, it should be mentioned that it is important to stop the culprit drug promptly.
- Sylvie added that the time relationship between adverse reaction and initiation of drug intake is important in assessing causality.
- Sarah suggested having the causality assessment chapter as an overarching chapter for all entities, and the group agreed.
- Sylvie asked where to include something on body surface area, suggesting maybe under Clinical Care.
- Sylvie said that the prevention aspect is also important, e.g. for high risk groups.
- The report should be addressed to regulators, clinicians, pharmaceutical companies, patients and scientists.
- He added that genetics is not just scientific question but a humanitarian question. The group agreed to include a section on genetic markers.
- Lee added that it was important to show how a successful partnership between clinicians, regulators, and the health ministry can drive a successful approach towards minimizing severe adverse reactions. – risk mitigation for everyone.
- Siew: communication from the health ministry for example is important.
- Neil suggested having a chapter on what is NOT SCARs. This will help industry.
- Sylvie asked about perhaps having another chapter on education.



- Ariel said that “diagnosis versus progression”, is important to state somewhere.
- Lee said it would be good to have a list of criteria to make it a lot clearer for people who run trials - Criteria for diagnostics.
- Sarah agreed with the proposal for a possible corticotropin-releasing factor (CRF) to capture all relevant diagnostic data, ideally one for all SCARs.
- Siew said that in Malaysia, they are using a CRF for SCARs.
- Lee thought there may be a need to define the main type of diseases we put under SCARs.
- Ariel said there was a need to talk about causality and assessment; it is very pharmacovigilance driven. He liked the idea of having parameters for making diagnoses and providing them in a table (not CRF or template), which would be helpful for everyone to understand what information is needed to make the diagnoses.
- Neil thought this was a good idea, and that pitfalls in diagnosis, due to some of the existing structures, should be added.
- Ariel said to mention that the MedDRA terms are a means of searching and not a means of diagnosing.