Guidelines for the RegiSCAR-Study

September 2009

PARTICIPATING CENTRES

Clinical teams

France

Prof. Jean-Claude Roujeau
Assistance Publique – Hôpitaux de Paris (APHP)
Service de Dermatologie
Hôpital Henri Mondor
51, Avenue du Maréchal de Lattre de Tassigny
F-94010 Créteil cedex
tel. +33 (1) 49 81 25 12
fax +33 (1) 49 81 45 04
e-mail: jean-claude.roujeau@hmn.aphp.fr

Germany

PD Dr. Maja Mockenhaupt
Dokumentationszentrum schwerer Hautreaktionen (dZh)
Universitäts-Hautklinik
Universitätsklinikum Freiburg
Hauptstr. 7
D-79104 Freiburg
tel. +49 761 270-6723
fax +49 761 270-6834
e-mail: dzh@uniklinik-freiburg.de

Italy

Dr. Luigi Naldi
Unità Operativa di Dermatologia
Azienda Ospedaliero Ospedali Riuniti di Bergamo
Largo Barozzi, 1
I-24128 Bergamo
tel. +39 035 400625
fax +39 035 253070
e-mail: luigi.naldi@gised.it

Netherlands

Dr. Sylvia Kardaun
Universitair Medisch Centrum Groningen (UMCG)
Afd. Dermatologie
De Brug 2 de verdieping K 2.063
NL-9700 RB Groningen
tel. +31 50 36 12 520
fax. +31 50 36 12 624
e-mail: s.h.kardaun@derm.umcg.nl

Data center

Prof. Martin Schumacher
Institut für Medizinische Biometrie und Informatik (IMBI)
Universitätsklinikum Freiburg
Stefan-Meier-Str. 26
D-79104 Freiburg
tel. +49 761 203-6661
fax +49 761 203-6680
e-mail: ms@imbi.uni-freiburg.de
e-mail: zks-regiscar@uniklinik-freiburg.de

Blood bank

Dr. Bijan Ghaleh
Biothèque du Centre d'Investigation Clinique
Plateforme de Ressources Biologiques
Hôpital Henri Mondor
51, Avenue du Maréchal de Lattre de Tassigny
F-94010 Créteil
tel. +33 1 49 81 37 86
fax +33-1-49 81 47 97
e-mail: bijan.ghaleh@inserm.fr

Webmaster

Ass.-Prof. Alexis Sidoroff
Universitätsklinik für Dermatologie und Venerologie
Medizinische Universität Innsbruck
Anichstr. 35
A-6020 Innsbruck
tel. +43 512 504 2971
fax +43 512 504 2990
e-mail: alexis.sidoroff@i-med.ac.at

REGISCAR EUROPEAN REGISTRY OF SEVERE CUTANEOUS ADVERSE REACTIONS (SCAR) TO DRUGS AND COLLECTION OF BIOLOGICAL SAMPLES

Objectives:

The aim of the study is to reduce the medical and economic burden of severe cutaneous adverse reactions (SCAR) on public health and to improve the safety of medication use. The practical objectives of this proposal are:

1) To build an European Registry of SCAR for continuous surveillance of new drugs with adequate pharmacoepidemiologic methodology and for providing reference information on SCAR
2) To organize a centralized collection of biological samples (plasma, lymphocytes, DNA and skin) to allow high quality studies on pharmacogenetics and investigations of the mechanisms of these reactions,
3) To constitute a cohort of 300 patients in order to study the outcome, prognosis factors, sequelae and impact on quality of life of these severe side effects of medicine. The recruitment for SJS/TEN was closed in March 2007. It is still going on for HSS/DRESS.

Brief description:

All cases of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) requiring admission in one of the hospital participating to the network in the participating countries are included in the study. Active case finding is used through regular contact with all relevant facilities. In each country a trained investigator interviews each case patient and collects information on medication use in the 4 weeks preceding the onset of the disease, recent infections, demographic information and relevant medical history. A standardized case record form (CRF) is used to collect prospectively clinical information up to the date of discharge or death, for HSS/DRESS also one year later. As done in previous studies an international group of experts will ascertain all cases using a strict process of validation.

With informed consent blood samples of the patients are sent to a specialized bank for separation and conservation of plasma, lymphocytes and DNA.
The clinical database will provide estimates of the risks of medications using case-control and case cross-over analyses as well as linkage to databases on drug utilization. It will also provide information on the outcome, allow the validation of prognosis indices, and give insights on the effect of treatments. Biological samples will be used for the following investigations: determination of the phenotype, functions and antigenic specificity of lymphocytes isolated at the time of the reaction from the blood and skin of patients; study of susceptibility genes by an association study directed first at candidate genes and second at the full genome by using 1000 single nucleotide polymorphisms (SNPs), determination of the serum level of a variety of cytokines that may have a prognostic value. Duplicates of biological samples and of the clinical database will be accessible to every scientist who has a project validated by an independent scientific board and the steering committee of the project.

Coordinator: PD Dr. Maja Mockenhaupt
Dokumentationszentrum schwerer Hautreaktionen (dZh)
Universitäts-Hautklinik
Hauptstr. 7
D-79104 Freiburg
Tel. +49 761 270-6723
Fax +49 761 270-6834
e-mail: dzh@uniklinik-freiburg.de

CASE SELECTION

According to the protocol, the national supervisor contacts each participating physician or institution regularly to ascertain potential cases of severe cutaneous adverse reactions (SCAR).

Inclusion criteria:

A potential case is defined as any patient diagnosed with SJS/TEN, AGEP or HSS/DRESS resulting in hospital admission or extension/complication of an inpatient episode.

Inclusion criteria for SJS/TEN

1. Hospitalization
2. Widespread exanthema with 1% or more detachment of epidermis OR more than one blister and mucous membrane involvement

Inclusion criteria for AGEP

1. Hospitalization
2. Acute pustular skin eruption (many pustules within a few days)

Except:
- Relapse of pustular psoriasis
- Localized or palmoplantar exanthema
- Exanthema with a clear infectious trigger (e.g. candida)
- Localized pustular contact dermatitis

Inclusion criteria for HSS/DRESS

1. Hospitalization
2. Acute onset of exanthema with fever >38°C
3. Enlarged lymph nodes
4. Involvement of at least one internal organ
5. Eosinophilia >10% or >700/µl or atypical lymphocytes or lymphopenia <4000 or lymphocytosis or thrombopenia

≥4 criteria must be fulfilled

Exclusion criteria

- acute pustular psoriasis
- epidermolysis bullosa
- EEM
- Kawasaki´s disease
- mechanobullous eruption (heat, cold, friction, pressure)
- pemphigus
- pemphigoid
- toxic shock syndrome
- vasculitis
- staphylococcal scalded skin syndrome (SSSS)

For every notification of a potential case, the interviewer has to enter the patient's data via RDE (remote data entry) into the data base (pages 1-3 plus cover sheet). Each potential case of SJS/TEN, AGEP and HSS/DRESS meeting the inclusion criteria should be visited by the local interviewer as soon as possible after case notification (within 5 days after case notification).

PROCEDURES AFTER CASE NOTIFICATION

- Arrange of the interview (see section Interview procedures on page 6 and Appendix D)

- For cases of SJS/TEN and HSS/DRESS try to organize a second drawing of blood samples with the patient at 8 ± 2 weeks after case notification.

- For cases of AGEP leave the AGEP follow-up record form with the treating physician and ask him to complete and return it.

- Send blood samples to CIC (see section sampling on page 8 and page 47). Complete the sample form correctly (take care of the correct interview number (see section CASE RECORD FORM-COVER SHEET on page 10) and send it to CIC together with the samples **(important: correct interview number should be written on each sample tube**). Send an e-mail to CIC (bijan.ghaleh@inserm.fr and christel.carbon@hmn.aphp.fr) to announce that a sample is on the way.

- Enter the first 3 pages of the CRF as well as the cover sheet into MACRO.

- Gather missing information from the family physician, family members etc.

- Stay in contact with the treating physician to get information about the maximum of erythema and of detachment. Ask the physician to send you copies of the laboratory findings from admission until discharge as well as copies of the medical chart (to complete the questions on therapy) and the discharge letter. For cases of AGEP the treating physician should complete the AGEP follow-up record form.

- After completion of the CRF enter the data via remote data entry (RDE) into the database.

8±2 weeks after case notification

For cases of SJS/TEN and HSS/DRESS organize a second blood sampling 8±2 weeks after case notification.

The second samples should be sent to CIC (see section sampling on page 8 and page 47). Send an e-mail to CIC (bijan.ghaleh@creteil.inserm.fr and christel.carbon@hmn.aphp.fr) to announce that a sample is on the way.

One year after case notification

Send the one-year-questionnaire to patients with HSS/DRESS one year after case notification. SF 36 is only required if the patient was at least 18 years old at the time of the onset of the SCAR.

INTERVIEW PROCEDURES

Conduct of the interview (see appendix D for a check list)

The tone of the interview is established by the interviewer. It is important to be unhurried and to show your interest in the person with whom you are speaking. A patient's right to privacy is of primary importance. In all instances reassurances must be given that his/her information will be kept confidential. In some instances this perception is out of your control. It is important to remember that this is not a negative reflection on you or your abilities.

Throughout the course of the interview it is important to provide a **time frame** (from the date of admission) for the patient. It may become necessary to repeat this frequently, especially if the patient becomes caught up in relating events that are not relevant to the questions being asked. It may be necessary to connect events for patients, such as when a patient mentions a condition that generally requires medication but there is no medication use forthcoming; and conversely, when the patient does not mention a specific condition yet reports medication use generally taken for that condition. Make sure that you obtain the correct information. When concluding an interview, thank the patient for his/her significant contribution to this study.

- **Things to remember**

In order to conduct and complete an interview properly all items listed below must be observed closely.

Prior to interview:

- If necessary, obtain permission from the individual physician to interview the patient.
- Consult with the appropriate hospital staff before approaching any patient in order to ascertain the patient's current status.
- Obtain consent of the patient to conduct the interview, in accordance with the rules and regulations in existence at each institution.
- Encourage the treating physician to take skin biopsies which will be used for histologic confirmation of the diagnosis. Ask the treating physician if it is possible to shock-freeze a part of the biopsy for research purposes. If possible try to get photographs of the histologic slides.

Preparation of forms before interview:

- **Enter identifying number/interview number on each page of the case record form** (see section CASE RECORD FORM-COVER SHEET on page 10). Be sure that the name of the patient is not on any sheet shown for the review.

During the interview:

- Before asking questions, you should explain to the patient what is the purpose of your visit and the interview. If possible, the patient should read the information leaflet about RegiSCAR and then sign the informed consent. If patients are not able to sign due to their illness, follow the rules made by the ethnical committee of your country.
- Ask for the address and/or phone number of the patient in order to be able to contact him/her before the follow-up sampling. There is space for this information in the informed consent.
- It is important that the forms are **neat, legible and complete**. DO NOT use abbreviations.

- When using additional pages enter the interview number in the boxes in the upper right-hand corner of each page.
- If the patient does not have all the information you need to complete the case record form, make sure you get the information from another source (e.g. general practitioner, family member etc.).

Immediately after interview:

- Check that all items are completed properly.
- Check that all brand names listed are spelled correctly.
- Check the type of application for each drug.
- Make copies of all lab values.
- Make copies of the hospital chart in order to complete pages 19-21 of the treatment.

After completion of the CRF

Enter the data into the data base.

SAMPLING

General comments on sampling

- Before collecting biological samples, **obtain informed consent of the patient**.
- If possible, try to get the following biological samples for each patient:
  Sterile blood (blood with EDTA, heparinated blood and blood without anticoagulant)
  Shock-frozen skin biopsy
- Each national center is responsible for organizing the shipment of blood samples to CIC.
- Frozen skin biopsies should be stored in each national center in liquid nitrogen or at –80°C in a freezer.

Sampling procedures for blood and blister fluid (See on page 44 and 47)

Blood samples shall be collected for all cases on the day of the interview. For SJS/TEN and HSS/DRESS try to get a second sample 8±2 weeks after the onset of the disease.

Complete the Sample form (see Appendix Sample Form on page 48)

Use the sample form for the first and second sampling and indicate on the sample form if it is the second blood sample.

Donor identification	Interview number: Provide the interview number (see section CASE RECORD FORM-COVER SHEET on page 10) Tick case or control. (At the moment no controls are collected.)
Sampling	Provide the date and the time when the sample was taken. Indicate the number of sample tubes and total volume for each type of sample.
Notes	If it is a second sample, please write in this box "**second sample"**
Shipment	Provide the date of shipment and the name of the courier.
Center taking the sample	Provide the name of the center taking the sample (e.g. in Germany it is always the Dokumentationszentrum schwerer Hautreaktionen (dZh), this may be different in other countries).
Investigator	Write your name in legible characters and sign the form.

Sampling procedures for frozen skin biopsies

The interviewer should encourage the treating physicians to take a skin biopsy which will be used on one hand for histologic confirmation of the diagnosis and on the other hand for research purposes. If the treating physician plans to take a biopsy, ask whether a part of the biopsy can be shock-frozen and kept at –80°C. The interviewer can transport the frozen skin biopsy on dry ice in an insulating box to the national study center and store it there in liquid nitrogen or at –80°C in a freezer until it is needed for research purposes. The biopsies should be taken as soon as possible. Indicate the date when the biopsy was performed and the localization. For all cases, biopsies should be taken from fresh lesions. For cases of SJS/TEN take the biopsy at the border of normal skin/target lesion or spot with blister, for cases of AGEP the biopsy should include a pustule.

CASE RECORD FORM (CRF)

General comments

The case record form contains:

General pages for all types of SCAR (page 1, 2, 3, 7-18)
Specific pages for SJS/TEN (pages 4A, 5A, 6A)
Specific pages for AGEP (pages 4B, 5B, 6B)
Specific pages for HSS/DRESS (pages 4C, 5C, 6C1, 6C2, 6 D1, 6D2, 6E1, 6E2, 6E3a, 6 E3b)
Specific pages for SJS/TEN and HSS/DRESS on therapy (page 19-21)

In general the majority of SCAR occurs in the community (community cases). However in up to 30% SCAR may develop during hospitalization for other conditions (in-hospital cases).

Note: date of admission on page 12-14 of the CRF:

For community cases the "date of admission" means the date of admission into the **first** hospital for treatment of SCAR.

For in-hospital cases the "admission" date is always considered as

- the date of the first cutaneous blister or mucous membrane erosion for SJS/TEN cases
- the date of the first pustule for AGEP cases
- the date of the first occurrence of a cutaneous eruption or, if no skin eruption was clearly seen, the diagnosis of eosinophilia for HSS/DRESS

COVER SHEET
FOR ALL CASES

Item	**Description**
Interview no.	This 7 digit number consists of a special code: the first and second digit indicate the national study center. The third digit is assigned personally to the investigator. The remaining four digits are consecutive numbers assigned to the cases/controls as they occur. The **numeration** of cases **starts with 0001**. Enter the interview number on each sheet of the CRF. Be careful to enter the same interview number on the sample form and on each sample tube.
SJS/TEN, AGEP, HSS/DRESS	Tick the corresponding type of SCAR; if you are not sure about the diagnosis, you may tick 2 boxes and complete the specific pages for both diseases.
This is a confidential ...	Provide name and address of your center.

CASE RECORD FORM
PAGE 1-PATIENT'S DATA
FOR ALL CASES

Note: Pages 1-3 as well as the cover sheet should be entered into MACRO always.

Item	**Description**
Initials of patient	Enter first letter of last name (family name) and first letter of forename.
Date of birth	Enter date of birth, day, month, year.
Age	For community cases enter the age at day of admission. For in-hospital cases enter the age at day of first sign of SCAR.
Death before interview	In case of death before interview tick "yes", otherwise tick "no".
Country of birth	Enter the country of birth in free text. Additional information on ethnic origin can be entered in the additional remarks (on page 18 in MACRO) if it is allowed by your ethnical committee.
Participation agreed to	Tick the corresponding boxes. There may be patients who agree to participate only in the registry, whereas others agree to participate in the registry, in the cohort study and in the genetic study.
Registry	Tick registry if the patient agrees to answer the first CRF.
Cohort study	Tick cohort study if the patient agrees to the follow-up (HSS/DRESS) or to a second blood sample (SJS/TEN).
Genetic study	Tick genetic study if there is informed consent for the genetic study according to the national legislation.

CASE RECORD FORM
PAGE 2-HOSPITAL DATA
FOR ALL CASES

Item	**Description**
Reporting hospital	The reporting hospital is the hospital/department notifying a case to the national study center. Provide the complete name of the reporting hospital/reporting department and enter the four digit code number (for hospital code number see Appendix C).
Treating hospital	Provide the complete name of the treating hospital/department and enter the four digit code number. Note: the treating hospital may be the same as the reporting hospital.
Date of admission	Refers to the date when the patient was admitted to the reporting hospital and treating hospital respectively. Note: on pages 12-14 of the CRF the date of admission refers to the date when the patient was admitted to **the first hospital because of SCAR** or when the first blister/mucosal erosion appears for in-hospital cases (see on page 9).
Date of notification	Enter day, month, year when the case was notified.
Date of interview	Enter day, month, year when the interview took place.
First hospital	If the patient has been transferred, write the complete name of the **first** hospital and complete the following information: Enter hospital name, date of admission and the four digit code for the hospital (see Appendix C). In case the patient was transferred more than once, provide only the details of the **first** hospital here. However, if there were one or more hospitals between the first and the reporting hospital, it might be useful to record them on a separate sheet, because they may be needed to obtain information on the course of the reaction.
Retrospective assessment	Tick “yes” if the interview takes place one month after discharge or death of the patient.
Development of skin reaction	Tick “prior to admission” if the adverse reaction occurred in the community leading to hospitalization. Tick “during in hospital stay” if the adverse reaction developed during hospitalization for another condition.

CASE RECORD FORM
PAGE 3-DIAGNOSES AND CLINICAL COURSE
FOR ALL CASES

Item	Description
Admission diagnoses	Three admission diagnoses may be listed. If there are more than three, select the immediate cause of admission. Enter only one diagnosis per line. Do not enter a procedure but the reason of the procedure (e.g. enter stomach cancer and not gastrectomy).
Date and clinical symptoms	Enter the course of the disease with dates and free text. Do not enter any drug name on this page because it will be used for determination of the index-day (the day of the onset of SCAR) and the review committee should not have any information on potential causes. Avoid also pieces of information open to suggest a specific drug (for instance: "discovery of high level of uric acid"- suggests allopurinol; "pneumocystis carinii"- suggests cotrimoxazole). Make sure the dates are compatible with dates given on the subsequent pages.
Fever	Fever is defined as a temperature above 37,5°C. Fill in the highest temperature in three digits (e.g. 39°C is 390). Enter without "," or ".". Provide the date of onset (day, month, year). For cases of SJS/TEN and AGEP the date of normalization is only to be filled in, if the fever was cured before admission. For cases of HSS/DRESS always provide the date of normalization, if possible. If there were two separate episodes of fever, fill in: Date of onset and date of normalization of the first episode, date of onset of the second episode. For date of normalization see description above. If there were more than two episodes of fever, explain in free text just above (with dates).

CASE RECORD FORM
PAGE 4A
FOR CASES OF SJS/TEN ONLY

Note: All items on the following pages refer to any occurrence prior to admission (or prior to onset of SCAR for cases developed in hospital).

Provide the date of normalization/resolution, only if the symptoms disappear before hospital admission for community cases or before the onset of SCAR for cases developed in hospital (see definitions on page 9).

Item	**Description**
Date of onset on pages 4A-6A:	Enter day, month and year.
Date of normalization	Provide date of normalization only if the symptoms disappear before hospital admission for community cases or before the onset of SCAR for in-hospital cases (see definitions on page 9)
Burning, pain	Tick "yes", if there was burning/pain. Please provide the date.
Pruritus	Tick "yes", if the patient complains about pruritus. Please provide the date.
Erythema, exanthema	Tick "yes", only if there was a skin eruption that was definitely not target-like and that resolved before appearance of target-like lesions or may still go on (e.g. erythema in psoriasis, eczema etc.). If spots and/or targets are confluent leading to large erythematous areas, this should not be checked here. Tick the corresponding box for the type of lesions. Please provide the date. Enter day, month and year.
Target lesions	Tick "yes", if there is any lesion common in SJS/TEN. Use definitions provided in the atlas and show the atlas pictures to the treating physicians, nurses and family members. It is possible to tick several types of target lesions (e.g. atypical targets flat and spots). Please provide the date. Enter day, month and year.
Blisters/erosions	Tick "yes", if there are blisters/erosions. Enter day, month and year.

Nikolski's sign	Tick "yes", if the Nikolski's sign is positive. Ask the treating physician for that. Enter day, month and year.
Epidermal sheets >5cm	Tick "yes", only if the epidermal sheets are >5cm. Enter day, month and year.
Localization of first blister/erosion	Specify in free text.
Maximum of erythema	Enter percentage of BSA (body surface area). Use the table provided in Appendix A to evaluate surface involvement (note: the surface of the patient's hand corresponds approximately to 1% BSA). If the interviewer sees the patient before the maximum of involvement, he must contact the treating physicians again in order to get the information.
Maximum of detachment	Enter percentage of BSA. Use the table provided in Appendix A to evaluate surface involvement (note: the surface of the patient's hand corresponds approximately to 1% BSA). If there is no detachment, enter 0% (in this case you do not have to provide a date). If the interviewer sees the patient before the maximum of involvement, he must contact the treating physicians again in order to get the information. Please do not write 10% or 30%. You have to decide if it is above or below in terms of classification.

CASE RECORD FORM
PAGE 5A-6A
FOR CASES OF SJS/TEN ONLY

Item	Description
Eyes	If the eyes were involved, tick "yes" and the corresponding items (e.g. stinging, redness, severe conjunctivitis/blepharitis). Several answers are possible. Severe conjunctivitis/blepharitis usually lasts for several days and requires ophthalmologic treatment. Only conjunctival injection, irritation or lacrimation is not a severe eye involvement. If the patient was seen by an ophthalmologist, tick "yes" and specify the diagnosis in free text.
Lips	If the lips were involved, tick "yes" and the corresponding items (e.g. burning, swelling, erosions). Several answers are possible.
Oral mucosa	If the oral mucosa was involved, tick "yes" and the corresponding items (e.g. burning, redness, erosions). Several answers are possible.
Genital mucosa	If the genital mucosa was involved, tick "yes" and the corresponding items (e.g. burning, redness, erosions). Several answers are possible. **Caution**: erosions on scrotum/labia majora are not mucosal erosions.
Erosions of other mucosa	Specify in free text which mucosae were involved (frequently nasal or anal mucosa, rarely bronchial mucosa).

CASE RECORD FORM
PAGE 4B
FOR CASES OF AGEP ONLY

Note: All items refer to any occurrence prior to the interview. Provide the date of normalization/resolution, if the symptoms disappear before interview, otherwise it will be asked for in the follow-up form.

It is important to provide the **date of normalization/resolution** for the following items (**pustules, erythema, desquamation**) on page 4B-5B (if resolution occurs before interview) or in the AGEP follow-up form.

Item	**Description**
Date of onset	Enter day, month and year.
Subjective symptoms (Burning, pain, pruritus)	You will get the information from the patient. Please provide the dates.
Erythema, exanthema	You will get information on the type and localization of erythema/exanthema from the treating physician or dermatologist. Several answers are possible.
Localization of exanthema	Please tick the corresponding box (see Appendix E).
Maximum extent of exanthema	Enter percentage of BSA. Use the table provided in Appendix A to evaluate surface involvement (note: the surface of the patient's hand corresponds approximately to 1% BSA). If the interviewer sees the patient before the maximum of involvement, he must contact the treating physician/dermatologist again in order to get the information.
Facial edema	Tick the corresponding box and provide the dates.

CASE RECORD FORM
PAGE 5B
FOR CASES OF AGEP ONLY

Item	**Description**
Date of onset	Enter day, month and year.
Pustules	Tick "yes", only if you see the pustules yourself or if they have been seen by an experienced dermatologist, otherwise tick "unknown". If you don't know the quantity or the morphology of the pustules, please enter "confirmed missing" into MACRO. There will be indicated "unknown" on the sheet for case review.
Localization of pustules	Several answers are possible.
Blisters/epidermal sheets >5cm	Tick "yes" only if the epidermal sheets are >5cm, otherwise tick "no". If yes, please enter percentage of BSA. Use the table provided in Appendix A to evaluate surface involvement. If the interviewer sees the patient before the maximum of involvement, he must contact the treating physicians/dermatologists again in order to get the information.
Maximum of detachment	Answering is only necessary if blisters/erosions appeared. Enter percentage of BSA
Postpustular desquamation	Tick "yes", if there is a postpustular desquamation.

CASE RECORD FORM
PAGE 6B
FOR CASES OF AGEP ONLY

Item	Description
Mucosal erosions	Tick "yes" according to the localization of erosions and provide the date of onset (day, month, year). Provide the date of normalization only if cured before interview.
Laboratory findings	Indicate the counts per µl on admission, the highest values and date of highest value. If the counts have not been done, tick the corresponding box. The highest leucocytes count may occur at a time after the first visit. In this case the treating physician should indicate it in the follow-up form.

CASE RECORD FORM
PAGE 4C-5C
FOR CASES HSS/DRESS ONLY

Note: All items on the following pages refer to any occurrence during the course of the disease.

Item	**Description**
Date of onset	Enter day, month and year.
Date of normalization	Enter day, month and year.
Burning, pain	Tick "yes", if there was burning/pain. Please provide the date.
Pruritus	Tick "yes", if the patient complains about pruritus. Please provide the date.
Exanthema	Several answers are possible.
Specific lesions	Tick "yes", if there were specific lesions and tick the corresponding type of lesion. Several answers are possible.
Blisters/erosions	Tick "yes", if there are blisters/erosions. Enter day, month and year.
Nikolski's sign	Tick "yes", if the Nikolski's sign is/was positive. Ask the treating physician for that. Enter day, month and year.
Maximum of erythema	Enter percentage of BSA. Use the table provided in Appendix A to evaluate surface involvement. (Note: the surface of the patient's hand corresponds approximately to 1% BSA). To get the maximum involvement, it may be necessary to follow the course of the case. Please do not write 50%, decide if it is below or above.

Information from	This question refers to exanthema and specific lesions. It is important to know the source of information. If the decision of skin lesions was made either by seeing the lesions directly or by seeing them on photographs, tick the corresponding box “investigator/photos”. If there was only written/descriptive information about skin lesions and the investigator has not seen any skin lesion himself, tick the corresponding box “chart”.
Maximum of detachment	Answering is only necessary if blisters/erosions appeared**.** Enter percentage of BSA. Use the table provided in Appendix A to evaluate surface involvement. To get the maximum involvement, it may be necessary to follow the course of the case.
Resolution of erythema/specific lesions $\geq$ 15 days	If you tick “yes”, please enter the date of resolution, if it is known.
Facial edema	If you tick “yes”, please enter the date of onset.
Mucosal symptoms	Specify in free text which mucosa is involved and which symptoms/lesions are present. Please provide the date.

CASE RECORD FORM
PAGE 6C1
FOR CASES HSS/DRESS ONLY

Note: On this page we ask for **acute organ involvement**, we do **not** ask for chronic or hereditary diseases.

Item	Description
Liver	Tick "yes", if there is any liver involvement. Specify in free text which symptoms/lesions are present or which diagnosis was made. For date of diagnosis, please provide day, month and year.
Jaundice	Tick "yes", if there is/was jaundice seen. For date of onset, please provide day, month and year.
Excessive alcohol intake	Tick the corresponding box. Tick "chronic" if the patient has been drinking high amounts of alcohol on a regular basis. Tick "acute", if the patient has currently been drinking or is still drinking excessively.
Kidney	Tick "yes", if there is any kidney involvement. Specify in free text which symptoms/lesions are present or which diagnosis was made. For date of diagnosis, please provide day, month and year.
Lung	Tick "yes", if there is any lung involvement. Specify in free text which symptoms/lesions are present or which diagnosis was made. For date of diagnosis, please provide day, month and year.
Dyspnea	Tick "yes", if the patient suffers from dyspnea. For date of diagnosis, please provide day, month and year.

CASE RECORD FORM
PAGE 6C2
FOR CASES HSS/DRESS ONLY

Note: For each item on this page the question that must be asked is:
Have you any problems with…?/ Do you suffer from…?

Item	Description
If yes, please specify	For some questions additional information is needed. Specify in free text which symptoms/lesions are present or which diagnosis was made.
Date of diagnosis	Enter day, month and year.
Date of onset	Enter day, month and year.
Other organ involvement	Please ask the patient as well as the treating physician if there is any other organ involvement. Specify in free text which symptoms/lesions are present or which diagnosis was made.

CASE RECORD FORM
PAGE 6D1-D2
FOR CASES HSS/DRESS ONLY

Item	Description
Date of performance	Enter day, month and year.
Have the following investigations been done?	All boxes should be completed. Not all investigations may have been done for each patient. In this case tick “no“. For retrospective cases it is not always certain whether the investigation was done. In that case tick “unknown“. If the investigation has been done, tick “normal“ or “abnormal“ concerning its results. For abnormal diagnostic results, specify in free text which symptoms/lesions are present or which diagnosis was made.

CASE RECORD FORM
PAGE 6E1-E2
FOR CASES HSS/DRESS ONLY

Item	Description
Date of sampling	Enter day, month, year.
Laboratory number	The laboratory number is unique for each lab. Start with number 1. If the laboratory does not change, the lab number will always be 1. If there is a change in the lab, use increasing numbers for each lab.
Value	Enter the value.
Lower limit	Enter the lower limits of the laboratory. This must be done only once for each lab.
Upper limit	Enter the upper limits of the laboratory. This must be done only once for each lab.
Unit	Please enter the unit being used. This must be done only once for each lab. There are some specifics: µg must be entered as microg 10^9 must be entered as 10x9 or 10E9 lab tests with results like negative/positive or present/not present must be entered as negative/not present= 0 positive/present= 1 In this case the limit is 0.
Bilirubin	Enter the total amount of bilirubin.
Other	If there are other abnormal values please enter these e.g. direct bilirubin, coagulation factors…

After saving the data you will be asked, whether you want to complete a further e-form. Go on for as many e-forms as you have dates of sampling. Remember to enter the right laboratory number and to enter new upper and lower limits after lab changes. Please enter all obtainable data for the whole course of the disease even if they are normal.

Special cases

There can be some special cases for a patient with HSS/DRESS concerning the lab values.

More than 5 "other" lab tests

Please enter the additional lab tests into an additional page with the same date. The corresponding lab number must be 100 plus the lab number of the previous page

Example: The patient had 12 other lab tests at the date 06/09/05 (only 1 laboratory was involved)
page 1: 1st 5 other lab tests are entered => lab number = 001, date 06/09/05
page 2: 2nd 5 other lab tests are entered => lab number = 101, date 06/09/05
page 3: 3rd 2 other lab tests are entered => lab number = 201, date 06/09/05

Multiple lab tests on the same day

Example: Urea was measured 3 times at the same date

1) The same limits and units are valid for all tests on that specific day.
The data entry should be restricted to the most interesting (i.e. highest/lowest) value, meaning only 1 value per test should be entered.

2) Change in limits/units
When there are multiple lab tests from different labs, you can use a further sheet to enter the data from the new lab. The lab number must be increased by 1.

Change in limits/units but no change in lab

In some circumstances the same lab provides different values for the same test using different limits/units, e.g. eosinophils once in /nl and once in %.
Please enter the values as if there was a change in lab, i.e. increase of the lab number by 1.

In general, the lab number should always be different if you enter data into an additional sheet with the same date of sampling!

CASE RECORD FORM
PAGE 6E3A-6E3B
FOR CASES HSS/DRESS ONLY

Have the following laboratory examinations been done?

Item	**Description**
n	no
y	yes
u	unknown
Date of sampling	Enter day, month and year.
Suggesting recent infection	Tick this box, if the result of the examination is suggestive for a recent including a possibly still present infection
Comments	Specify in free text results, method, titer etc.
other	Enter other parameters not mentioned in the questionnaire but done in your patient, e.g. measles.

CASE RECORD FORM
PAGE 7-FURTHER INFORMATION FOR CASE VALIDATION
FOR ALL CASES

Item	Description
Photographs	Clinical photographs of the patient are very important in confirming the case. When visiting the patient, take photographs: overview pictures (front and back) to get a good estimation of the BSA involved and close-ups of the lesions. Ask the treating physician whether there are photographs from an earlier or later stage of the disease. In case of iterative photographs enter up to 3 dates in the line "further photographs" .
Biopsy	Encourage the treating physician to take skin biopsies: one for histologic confirmation of the diagnosis and one shock-frozen biopsy for research purposes. The best pathologic slides for confirmation of the diagnosis are those taken within 24 hours of the development of the lesion. Request the histological findings. Try to get photographs of the pathologic slides for each patient. Note: For all cases, biopsies should be taken from fresh lesions, for cases of SJS/TEN take the biopsy at the border of normal skin/target lesion or spot with blister. For cases of AGEP the biopsy should contain a pustule. All photographs, both clinical and histological, should be labeled with the interview-number of the patient and the date when they were taken.
Diagnosis by a dermatologist	Enter date of diagnosis; specify diagnosis in free text.
SCORTEN-Parameters	The information for these parameters are only collected for SJS/TEN. It is not necessary for AGEP and HSS/DRESS. SCORTEN-parameters may not have been investigated for all patients. In this case tick "not done". If the values are above the indicated limits within three days after admission tick "yes" and provide the highest value, otherwise tick "no". If the values are below (bicarbonate) the indicated limits within three days after admission tick "yes" and provide the lowest value, otherwise tick "no". For in-hospital cases: "admission" should be changed into - "first cutaneous blister or mucous membrane erosion" for SJS/TEN cases

CASE RECORD FORM
PAGE 8-SYMPTOMS/EVENTS WITHIN 1 MONTH BEFORE THE RECENT SKIN REACTION
FOR ALL CASES

Note: All items on this page refer to any occurrence in the 4 weeks prior to admission (or prior to onset of SCAR for cases developed in hospital).

Item	**Description**
Herpes labialis or fever blisters	A diagnosis requires the reporting of the typical grouped blisters followed by crusts. Enter day, month, year of onset of recent eruption and enter day, month, year of normalization.
Do you have recurrent herpes labialis or fever blisters?	Tick "yes", if the patient reports an eruption in the time prior to 1 month before admission. Enter day, month and year of last eruption.
Herpes genitalis	A diagnosis of genital herpes should be accepted only if it was confirmed by a doctor.
Do you have recurrent genital herpes?	A diagnosis by a doctor during a previous episode is also acceptable. Tick "yes", if the patient reports an eruption in the time prior to 1 month before admission. Enter day, month and year of last eruption.

CASE RECORD FORM
PAGE 9-SYMPTOMS/EVENTS WITHIN 1 MONTH BEFORE THE RECENT SKIN REACTION
FOR ALL CASES

Note 1: All items on this page refer to any occurrence in the 4 weeks prior to admission (or prior to onset of SCAR for cases developed in hospital).

Note 2: Questions on recent infections should be asked by sentences on symptoms, rather than on medical diagnoses (e.g. diarrhea, cough, sputum, runny nose, nasal congestion, sore throat, myalgia, earache, urinary burning, frequency/urgency, suprapelvic pain).

Item	**Description**
Influenza/influenza-like illness	Since viral confirmation of influenza is most often not available, the diagnosis of clinical influenza requires an acute onset of fever >38,5°C, concomitant with respiratory symptoms and muscle aches.
Rhinopharyngitis/common cold	A diagnosis requires the reporting of runny nose, nasal congestion not attributable to other non-infectious causes (e.g. allergic rhinitis, vasomotor rhinitis). It is frequently accompanied by sore throat and occurs in outbreaks in winter.
Tonsillitis	A diagnosis requires the reporting of acute onset of sore throat and/or dysphagia with fever >37,5°C and putrid deposits on the tonsillae.
Sinusitis	A diagnosis requires headache or facial pain and/or tenderness of the sinus and putrid discharge (pyorrhea).
Acute otitis	A diagnosis requires earache of acute onset with fever >37,5°C.
Acute bronchitis	A diagnosis requires the reporting of cough and sputum accompanied by fever >37,5°C.
Pneumonia	A diagnosis should be accepted only if it was confirmed by a doctor.

Acute gastroenteritis	A diagnosis requires the reporting of acute onset of diarrhea (loose stools with a frequency greater than 3 times a day) accompanied by fever >37,5°C. Nausea and vomiting are frequent additional symptoms.
Acute cystitis	A diagnosis requires the reporting of at least two of the following symptoms: dysuria, changes in frequency, urgency, suprapubic pain. Specify if a bacterial infection has been proven, or if there was a prior cystitis. If you cannot obtain that information tick "unobtainable" in MACRO.
Other infections	If appropriate, specify in free text the nature of the other infection(s), and the corresponding dates of onset and of normalization.
HIV-status	"Yes" and "no" should be filled only if a serologic test for HIV has been performed within one year. For all other instances, fill "unknown". Knowledge of HIV status is very useful in the context of SJS/TEN. If the HIV-status is known, this information will be treated anonymously as all other items.
AIDS	The diagnosis is made according to CDC-criteria by the treating physician. Thus, AIDS should be usually "yes" or "no" in HIV-infected patients.

CASE RECORD FORM
PAGE 10-11
HAVE YOU IN THE PAST HAD ANY OF THE FOLLOWING DISEASES?

Item	Description
Year of event	If the patient answers "yes" to the question "Have you in the past had any of the following... ", then ask, when it first occurred and enter the year of event in the boxes provided (e.g. 98, if occurred in 1998, or 07, if occurred in 2007). If this information is missing, leave the boxes blank (click unobtainable in MACRO).
Have you had in the past.....?	All boxes should be completed. Note: For some questions additional information is needed, e.g. if response to "severe liver disorders" is "yes", specify in free text which diagnosis was made. **SCAR** means erythema exsudativum multiforme majus (EEMM), SJS/TEN, AGEP or HSS/DRESS. On this page we ask for **chronic** or **hereditary** liver and/or kidney disorders. We do **not** ask for acute involvement related to SCAR (e.g. transient abnormal liver enzymes). A malignant diseases/cancer is defined either by the date of diagnoses or present therapy. It should be diagnosed within two years from the acute severe skin reaction (year of reaction – year of cancer diagnosis ≤ 2) If the malignant disease is still under therapy (drugs or radiation therapy) the date of diagnosis could date back more than two years. Please do not mix up rheumatoid poly-arthritis with degenerative diseases like arthrosis. If you tick "yes" for "X-rays or radiation therapy", specify the date of most recent therapy (enter day, month, year), and the indication for X-rays. Remember we ask for therapeutically **not** diagnostic indication.

CASE RECORD FORM
PAGE 12-14
MEDICATION HISTORY WITHIN 1 MONTH BEFORE HOSPITALIZATION
FOR ALL CASES

Pages 12-14 are used in conjunction with Appendices B-1 to B-5

Appendix B-1

Part 1. Statement to be read to all persons being interviewed
Part 2. Questions to be asked to all persons being interviewed

Appendix B-2 (List of indications for drug use)

Appendix B-3 (List of drug names)

Based on this list of drug names, a list of specific brand names should be prepared in each country.

Appendix B-4

Codes for type of application
Codes for frequency

Pages 12-14: "Medication history within 1 month before hospitalization", are to be used to record all drug usage for:

1. 4 weeks prior to admission (8 weeks for cases with one of the drugs being on the list of suspected drugs newly introduced in the market, see Appendix B-5)
2. Any continuation of this drug usage
3. Any prior use of the drug recorded
4. Any previous adverse reactions to the drug
5. Dosage information

- Before the interview is conducted, make a list from the patient's medical record of all medications taken prior to admission. Furthermore, it is useful to ask the patient to name all drugs he/she used in the last month. Record the names and when the patient finished, proceed with the details as described.

- Read the statement provided in Appendix B-1 to each person being interviewed.

- The questions listed in Appendix B-1 must be asked, in entirety, to all persons being interviewed.

  - **Part 1.** of this question is asked before each group of indication listed. This question should also be interjected at any point where clarification or reinforcement seems necessary.
  - **Part 2.** of this question is asked before each group of specific drug product listed. This question should also be interjected at any point where clarification or reinforcement seems necessary.

- Drugs are only to be recorded if used within 4 weeks before admission.
  (8 weeks for cases with a drug of the list of suspected drugs newly introduced in the market, see Appendix B-5).

CASE RECORD FORM
PAGE 12-14
MEDICATION HISTORY WITHIN 1 MONTH BEFORE HOSPITALIZATION
FOR ALL CASES

Item	**Description**
Date of admission	Community cases: enter the date of admission into the first hospital for treatment of SCAR. For in-hospital cases: "admission" should be changed into - "first cutaneous blister or mucous membrane erosion" for SJS/TEN cases - "first pustule" for AGEP cases - "first occurrence of a cutaneous eruption or, if no skin eruption was clearly seen ,the diagnosis of eosinophilia" for HSS/DRESS
No drug use	If a patient denies all medication use in the month prior to admission, tick the box: "no drug use" at the top of page 12.
Drug (Brand name in MACRO)	Enter in free text the complete brand name of the drug. Print the drug name legibly. Check the active substance of your "brand drug" and enter it into MACRO under the headline "drug". This information appears only in MACRO not in the paper version of the questionnaire. It is your responsibility to check the correct spelling for all entries. If the indication for a drug changes, e.g., if a patient takes "aspirin" normally as a blood thinner and responded to take "aspirin" as well for headache, record "aspirin" twice (separate for each indication). Be sure to record all exposures for that drug. If the drug name is unknown, enter "unknown" in the space provided for the name. When the indication is known and the drug name is unknown, enter "unknown" followed by the specific indication; e.g. indication is constipation. If an unknown laxative was used, enter "unknown laxative".
Indication	This is a field to be completed in free text (in English only).
Dose	Enter in free text the daily dose of the drug, specifying the units used.
Type of application	Use the code numbers provided, record the form in which the drug was used/taken by the patient. The list of types of applications is given in Appendix B-4.

Date of begin of intake	Whenever the use of the drug began within 4 weeks prior to admission or earlier, this field should be fully completed. (8 weeks for cases with a drug of the list of new suspected drugs, see Appendix B-5). Enter the exact date by referring to a calendar. If the exact day is not known, but the week is known, enter the first day of the week. If the exact week is not known between two or three or more, enter the earlier previous possible date; e.g. in case of hesitation between two weeks ago and three weeks ago, the first day of three weeks ago should be selected. In case of multiple treatments with the same drug during the past month, it is possible to complete three dates of begin of intake. If there were more than 3 treatments during the past month, use two or more successive tables for the same drug.
Date of end of intake	Date of last intake is obtained by asking the patient the day the medication was last used prior to admission. This field should be fully completed. Enter the exact date, by referring to a calendar. If exact date is not known, use the same procedure as for the date of "begin of intake" (see description above). In case of multiple treatments with the same drug during the past month, it is possible to complete three dates of end of intake. **This should be completed. Take particular attention for anticonvulsants, in case of progressive increase in dosage. If more than 3 different dosages have been taken during the past month, use two successive tables for the same drug.** If the intake of a drug is ongoing, end of intake should be entered as 1 day after the interview.
Frequency	Enter the appropriate code in the box provided. The list of the frequency codes is provided in Appendix B-4
Previous intake	The question to be asked is whether the patient has ever used this medication at any other time in his/her life. If the answer is "yes", ask for adverse reactions.
Adverse reactions	If "yes", specify in free text the type of reaction.

CASE RECORD FORM
PAGE 15
HAVE YOU EVER HAD AN ADVERSE REACTION TO DRUGS
FOR ALL CASES

Ask the patient if he/she ever had an adverse reaction to drugs.
If "yes", write down the drug name and the type of reaction.

Ask the patient, whether you may contact the family physician to get more detailed information on prior adverse drug reactions. Do not enter usual symptoms such as diarrhea after the use of antibiotics.

CASE RECORD FORM
PAGE 16-DISCHARGE SHEET
FOR ALL CASES

Item	Description
Hospital no.	Enter the number assigned to the hospital. Enter the four digit code number.
Discharge diagnoses	List the diagnoses as they appear on the discharge summary. First enter those which were most relevant to the admission. Diagnoses preceded by "History of" or "Status post" should be excluded unless applicable to this admission. Definitive diagnoses should be listed before any that are "possible", "probable", "ruled out", or "question of". If no list is provided in the summary, select the pertinent diagnoses and place them in order of importance. There is space for five diagnoses to be listed. If there are more than five diagnoses in the summary, select the ones most pertinent to the admission.
Death	In case of death at hospital, tick the appropriate box, and enter the date of death.
Discharge	In case of discharge from the hospital, tick the appropriate box, and enter the date of discharge.
Mycoplasma infection	In case of mycoplasma infection within two months before admission to the hospital (or before the onset of the disease), tick the appropriate box, and enter the date of diagnosis. Tick also the appropriate box for criteria used for diagnosis. If the infection occurred before admission, but diagnosed in hospital you have to tick "yes" respectively.

CASE RECORD FORM
PAGE 17
MAIN SOURCE OF INFORMATION
FOR ALL CASES

Item	**Description**
Clinical pattern of the reaction	If skin lesions were not seen by the investigator in the acute stage, provide the source in free text.
Medication history	The choice has to be made whether information on medication history was obtained by "just the patient", "just other sources" or "both" meaning patient and other sources. "Other sources" are a medical chart, the family physician, family members, pharmacists…
Unit of treatment	Specify the type of unit by ticking the appropriate box. Several answers are possible.

CASE RECORD FORM
PAGE 18
ADDITIONAL REMARKS
FOR ALL CASES

All important additional information which is not mentioned in the CRF can be entered here. For example some countries are allowed by their ethnical committee to ask for the country of birth of the patient's father or grandfather. You can add any information about death after discharge or why a second blood sampling cannot be done for a special case. If there is nothing to add, you can leave this page empty.

CASE RECORD FORM
PAGES 19-21
QUESTIONS ON TREATMENT OF SCAR

The questionnaire on treatment should be completed for all cases of SJS/TEN and HSS/DRESS, even if the patient died**.**

General remarks

This study is based on the original medication chart of the first four days of each patient in the cohort in every hospital or department, in which the patient was treated for SCAR within 42 days after the onset of the reaction. Copies of the original medication chart have to be obtained by each team. The necessary information should be extracted to complete the questionnaire. If a copy of the original medication chart is not available from the treating hospital, an investigator has to visit the hospital and complete the questionnaire directly in the hospital or department.
If the patient was transferred either to a different hospital or to a different department within the same hospital, a new questionnaire, pages 19-21 respectively, has to be completed. In case of several transfers this may lead to several treatment questionnaire pages for the same patient, each indicating the treatment in each hospital/department up to seven days. The sheets of each questionnaire of the patient in each department should be clearly identifiable by a number. If you have completed a single therapy page by mistake, e.g. by entering data twice, please delete or set to missing each single entry on that page in MACRO. Only if all items are deleted or set to missing, the data center can be sure that there are no mistakes anymore. Please note that it is not possible to delete the complete page of e-form.

Interview number and numbering of therapy questionnaire

Indicate the seven-digit interview number to identify the case. Below the interview number is a single additional box. Here must be indicated whether this is the first, second, third (1, 2, 3, ...) hospital/department for treatment of the patient. Please note that the therapy data which are collected on a **set** of 3 single pages (19-21). Enter the unique number on **each** page 19-21, even if the patient is not transferred (in this case it is "1"on each page 19-21).

Date of admission

Attention: The date of admission into the treating hospital/department is the date of admission, even for in-hospital cases. Normally you have different dates for date of admission, if the patient is transferred. There is only one exception, when the patient is transferred more than once on the same day.

Treating hospital

Provide the complete name of the treating hospital and enter the four digit code number (for hospital code number see Appendix C).
Department: Tick only one department. If the patient is transferred to another department within the same hospital, e.g. from dermatology to the intensive care unit, provide a new set of therapy pages (19-21) for the new department.

Systemic therapy

We are only interested in systemic treatment with immuno-modulating agents like corticosteroids, intravenous immunoglobulins, cyclophosphamide, cyclosporine, pentoxifylline, plasmapheresis, and antibiotics independent of the indication of these drugs.

Starting date

Date of day 1. Starting date should be within 7 days after admission to this specific department. Enter day, month, year.

Stopping date

Provide the exact date of last use, if this treatment was discontinued within seven days after admission to this hospital. If the treatment was stopped later and you don't know the exact date, leave the box for "stopping date" empty and tick "unobtainable" in MACRO.

Corticosteroids

Only systemic corticosteroids, not topical corticosteroids or corticosteroids for inhalative use should be mentioned. Therefore, application can be only i.v. or p.o. Dosage is usually mg or g (total dosage) or mg/kg body weight. We collect data for steroid use independent from the indication (e.g. high doses of steroids used in septic shock).

IVIG

Unit of dosage is g/kg body weight.

Other systemic treatments

Other systemic treatments of interest are immuno-modulating agents (e.g. cyclophosphamide, cyclosporine, pentoxifylline, plasmapheresis etc.).

Antibiotics

Antibiotics are defined as antibacterials for systemic use (ATC-class J01). Each team will get a list of these drugs. We collect data for antibiotic use independent from the indication. The time window is date of admission in the department plus seven days. Prophylactic use means treatment with antibiotics to avoid possible infections which can be caused by complications of SCAR. Therapeutic use means treatment of existing infections. This is independent from the beginning of the infection in relation to the index day or day of admission.

Transfer to other hospital or department for treatment of SCAR

Usually, the patient is transferred because of progression of SCAR or because an underlying disease requires a specific treatment. Tick yes, whenever the patient is transferred to another department even within the same hospital. In case the patient is transferred although he/she does not need further treatment for SCAR, e.g. transfer from intensive care to a general internal medicine department or to a rehabilitation center, tick no. No further therapy questionnaire is needed.

CASES DEVELOPED IN HOSPITAL

Development of a case during in-hospital stay is defined as a patient who is admitted to a hospital for an unrelated condition and in course of the hospitalization develops a severe skin reaction which meets the inclusion criteria of the study. The patient should be in hospital for more than two days before the adverse reaction occurs. If the reaction occurs in the first two days after admission, it might have started even before admission and the patient is considered a "community case"

The method of acquiring information of these cases differs.

The information on medication history of these cases will be obtained partly by record review. As information on medication is needed for 1 month prior to the index-day, you must try to get all information on the patient's medication before hospitalization. (For cases with a drug of the list of suspected drugs newly introduced in the market, see Appendix B-5, you must obtain the medication history for 8 weeks before the beginning of the severe skin reaction.)

The standard interview form can be used with the following modifications:

Item	**Description**
Page 3 Clinical symptoms	A brief course leading to the initial reason for hospitalization should be followed by a description of the hospital course leading up to the diagnosis of the cutaneous reaction. Enter the course of the disease with dates and free text. Do not enter any drug name on this page because it will be used for determination of the index-day (the day of onset of SCAR) and the review committee should not have any information on potential causes. Avoid also pieces of information open to suggest a specific drug (for instance: "discovery of high level of uric acid"- suggests allopurinol; "pneumocystis carinii"- suggests cotrimoxazole). Make sure the dates are compatible with dates given on subsequent pages.
Page 12-14	"admission" should be changed for - "first cutaneous blister or mucous membrane erosion" for SJS/TEN cases - "first pustule" for AGEP cases - "first occurrence of a cutaneous eruption or, if no skin eruption was clearly seen ,the diagnosis of eosinophilia" for HSS/DRESS Example: If a patient was admitted to the hospital on June 1 and met study criteria on June 10, the reference date would be June 10.

FATAL CASES

If a patient dies before an interview is conducted, the data should be collected by record review. The standard case record form should be used exactly in the same way as for survivors. Try to get as much detailed information as possible.

8±2 WEEKS FOLLOW-UP BLOOD SAMPLE FOR SJS/TEN AND HSS/DRESS

General comments

The follow-up blood sampling of patients with SJS/TEN and HSS/DRESS should take place 8±2 weeks after case notification.

When ascertaining a case, make sure to get the address and the phone number of the patient (space is provided in the informed consent) in order to be able to contact him/her to make an appointment. The follow-up sampling can take place e.g. at the treating/reporting hospital or at the family physician's office.

Note: You can already start completing pages 19-21 (pages with questions on treatment of SJS/TEN and HSS/DRESS) at the time of the first interview.

Blood sampling at 8±2 weeks

The following samples should be taken:

Adults: 2x7ml with heparin/citrate and 1x7ml with anticoagulant
Children: 2x7ml with heparin/citrate and 1x5ml with anticoagulant

Check with CIC if any further EDTA sample (in case there were problems with DNA extraction from the first sample) is required.

Patient died before follow-up

If a patient dies before the second blood sampling takes place, write a short note on the "additional remarks" page.

AGEP
FOLLOW-UP

General Comments

If necessary, each national center should translate the follow-up record form for AGEP into the national language, as this record form should be completed by the local physicians.

When the interviewer visits an AGEP-patient, he/she should ask the treating physician to complete the AGEP-follow-up record form and send it with the discharge letter to the national study center.

The treating physician needs to provide only information that is not already included in the discharge letter. The interviewer has to enter the data into MACRO, no matter if they are written in the discharge letter or on the AGEP sheet.

HSS/DRESS
1 YEAR FOLLOW-UP

One year after the onset of the disease the patient receives a 1 year follow-up questionnaire and the SF 36 via post. SF 36 is only required if the patient was 18 years old at the time of the onset of HSS/DRESS. Do not forget to send it.

If you don't get the questionnaires back please enter that into MACRO ("additional remarks") and provide an explanation.

REGISCAR: SEVERE CUTANEUS ADVERSE REACTIONS

SAMPLE FOR RESEARCH PURPOSES

BIOLOGICAL SAMPLES

• Sterile blood

Type of sample	CASES				CONTROLS
	1st sampling < day 5		2nd sampling ** (4-8 weeks after notification)		
	Adults	Children	Adults	Children	
With EDTA	2 x 7 ml	1 x 7 ml *	-	-	2 x 7 ml
With heparin	2 x 7 ml	2 x 7 ml	2 x 7 ml	2 x 7 ml	-
Without anticoagulant/serum	1 x 7 ml	1 x 5 ml	1 x 7 ml	1 x 5 ml	-

* at least 5 ml

** except for AGEP

LABELING

Interview number

Don't use labels allowing the donor identification

CONSERVATION

All samples: at room temperature

SHIPMENT

• At room temperature
• As soon as possible after sampling
• In insulated secured packages for diagnostic specimens conform to the IATA regulation
• Join the "Sample form" with all requested information (EN.T01.REC.07)
• By air courier: samples should reach CIC within 48 hours of collection (in any case not more than 72 hours). They should arrive to CIC before Friday 2 p.m.
• Notify the shipment and the air bill tracking number preferably by e-mail to (bijan.ghaleh@inserm.fr and christel.carbon@hmn.aphp.fr)

ADDRESS OF SHIPMENT:

Biothèque du Centre d'Investigation Clinique (CIC)

Plateforme de Ressources Biologiques
Hopital Henri Mondor
51 avenue du Marechal de Lattre de Tassigny
94000 Creteil
France

CONTACT :

Tel. : +33-1-49 81 37 86

Fax : +33-1-49 81 47 97

SAMPLE FORM

RegiSCAR: severe cutaneous adverse reactions

SAMPLE FOR RESEARCH PURPOSES

Please fill in all information requested below

DONOR IDENTIFICATION

Interview no : ☐☐☐ ☐☐☐☐ **Case** ☐ **Control** ☐

SAMPLING

Date : _/_/ _/_/ _/_/ **Time :** _/_/:_/_/

Type of sample	Number of tubes	Total volume	Notes
☐ blood with EDTA			
☐ blood with heparin			
☐ blood without anticoagulant/serum			

SHIPMENT

Date : _/_/ _/_/ _/_/

Dispatched by :

CENTER TAKING THE SAMPLE

Hospital / Department :

Address :

Telephone : **Fax :**

Reserved to the investigator

I certify that I received the signed informed consent from the donor.

Name : **Signature :**

Reserved for the service of reception and treatment of biological samples

Name :……

Date : _/_/ _/_/ _/_/ **Time :** _/_/:_/_/

Remarks :

APPENDIX A
BURN ESTIMATE AND DIAGRAMM
AGE VS AREA

Area (% of BSA)	Birth-1 year	1-4 years	5-9 years	10-14 years	15 years	Adult	Erythema	Blisters Erosions
Head	19	17	13	11	9	7		
Neck	2	2	2	2	2	2		
Ant. Trunk	13	13	13	13	13	13		
Post. Trunk	13	13	13	13	13	13		
R. Buttock	2,5	2,5	2,5	2,5	2,5	2,5		
L. Buttock	2,5	2,5	2,5	2,5	2,5	2,5		
Genitalia	1	1	1	1	1	1		
R. Upper Arm	4	4	4	4	4	4		
L. Upper Arm	4	4	4	4	4	4		
R. Lower Arm	3	3	3	3	3	3		
L. Lower Arm	3	3	3	3	3	3		
R. Hand	2,5	2,5	2,5	2,5	2,5	2,5		
L. Hand	2,5	2,5	2,5	2,5	2,5	2,5		
R. Thigh	5,5	6,5	8	8,5	9	9,5		
L. Thigh	5,5	6,5	8	8,5	9	9,5		
R. Leg	5	5	5,5	6	6,5	7		
L. Leg	5	5	5,5	6	6,5	7		
R. Foot	3,5	3,5	3,5	3,5	3,5	3,5		
L. Foot	3,5	3,5	3,5	3,5	3,5	3,5		

APPENDIX B-1
MEDICATION HISTORY (STATEMENTS TO BE READ)

Statement to be read to all persons being interviewed:

We are interested in obtaining information on all the medications which you were taking at the time you came into the hospital, as well as any medications which have been taken in the four weeks prior to your admission. (8 weeks for cases with a drug of the list of suspected drugs newly introduced in the market, see Appendix B-5)
These include medicines which you may have obtained anywhere, including a doctor's prescription, a hospital, a pharmacy, a supermarket, a store, a nurse, a homeopath, an alternative practitioner, a friend, a neighbour and/or a relative.

Questions to be asked to all persons being interviewed:

Before you came into the hospital or at any time during the past month, have you used: (during the past two months for cases with a drug of the list of suspected drugs newly introduced in the market, see Appendix B-5)

Part 1. any medications for the following indications ?

Part 2. any of the following specific medications ?

APPENDIX B-2
MEDICATION HISTORY INDICATION SHEET

Pain-headache-backache
Muscle relaxant - spasms - swelling
Arthritis - gout - high uric acid
Fever - cough - cold
Antibiotic - sulfonamides
Tremors - seizures - anticonvulsants
Tranquilizers - emotional disorders - psychiatric conditions
Sleeping medications
Menstrual problems or gynecological conditions
Oral contraceptives
Menopause - change of life
Other hormones - steroids - cortisone
Fluid retention
Heart condition - angina
Blood pressure
Blood thinners - anticoagulants
Diabetes
Thyroid conditions
Weight control
Laxatives - antidiarrheals
Nausea - dizziness - vertigo
Stomach - ulcers - bowel
Allergy
Asthma - breathing difficulties
Skin disease
Antitumor - chemotherapy
Anemia - iron - vitamins
Other

APPENDIX B-3
DRUG NAME LIST

Trade name should be listed for the patient; this list is written in each country under the responsibility of the national supervisor. Although trade names may differ from one country to another, the list of generic drug names should be the same in all countries, and read in the same order.

Generic names	Brand names
Allopurinol	To be completed in each country the list should be limited to 40 to 60 brand names covering ≥
Aminopenicillins	70 % of the national market
Sulfonamides:	
Cotrimoxazole	
Sulfadiazine	
Sulfasalzine	
Antiepileptic drugs:	
Carbamazepine	
Oxcarbazepine	
Phenytoin	
Phenobarbital	
Lamotrigine	
NSAIDS:	
Oxicam-NSAIDS	
Phenylbutazone	
Indometacin	
Naproxen	
Ketoprofen	
Ibuprofen	
Diclofenac	
others	
Nevirapine	
Dapsone	
Diltiazem	
Minocycline	
Terbinafine	
Chloroquine	

APPENDIX B-4

Codes for type of application

81 p.o. (tablet, capsule), sublingual

82 i.m., s.c., intrapleural, intrathecal, intraarticular, antiseptic in wound cavity

83 suppository

84 local application like eye, ear, nose, mouth, pharynx, anal or genital mucosa (e.g. ear, eye or nose drops, nose spray)

85 transdermal

86 p.o. liquid (sucking tablet, effervescent tablet)

87 i.v.

88 topical (cream, powder, ointment, plaster)

89 inhalation

Codes for frequency

1 one day per week

2 every other day

3 2-3 days per week

4 4-6 days per week

7 daily

9 unknown

APPENDIX B-5
LIST OF SUSPECTED DRUGS NEWLY INTRODUCED IN THE MARKET

If one of the following drugs has been taken by a patient with SCAR, you should ask for **symptoms/events (on pages 8 and 9)** as well as for **all medication (on pages 12-14)** taken **within 2 months** before the recent skin reaction.

COX-2 Inhibitors (rofecoxib, celecoxib, valdecoxib)

Leflunomide

Sertraline

APPENDIX C
ASSIGNING HOSPITAL CODE NUMBERS

As each national study center develops a network of contact hospitals, a code number should be assigned to each institution for the purpose of identification. The hospital code number consists of four digits.

These numbers should be assigned at the national level and a list of names with code numbers sent to the RegiSCAR Data Center. Periodically, as new hospitals are added to the list, a revised edition should be sent.

APPENDIX D
CONDUCTING THE INTERVIEW
CHECK LIST

Arrangement of the visit

Phone-call
Time to visit (change of dressings)
Organization of visit (e.g. transfer of the patient to another unit - child or patient in poor condition - family member, foreign patient - interpreter)
Blood
Skin biopsy

Material needed for the interview

Visiting-card for identification
White coat with name badge
Photo camera (additional films)
Informed consent (upon national regulations)
Drug information list and drug name list
Drug dictionary (e.g. “Red List” in Germany)
Instruction manual
Atlas
Case record forms (additional pages 12, for medication history)
Follow-up record form for AGEP

Material for shipment of blood samples

Dry ice for transport of frozen skin biopsy

Material needed for information

Leaflet about the activities of the study center
Leaflet with information on the disease
Literature

Interview

Get the address and/or phone number of the patient in order to contact him/her for the follow-up sampling (on informed consent).

APPENDIX E
CASE REVIEW

Check for all cases before review

All obtained data must be entered completely into MACRO. For the clinical review at least the specific pages 1-7 are necessary. Nevertheless it is important for the study to obtain a complete data set. Based on the data entry the data center (AGEP, HSS/DRESS) or the dZh (SJS/TEN) will provide clinical sheets (and flow charts for HSS/DRESS) for each case which will be reviewed. The interviewer has to check whether the clinical sheets are correct or not. If there is something missing or wrong, changes have to be done in MACRO and the data center/dZh must be informed. On request the data center/dZh will send an updated version of the clinical sheets after the changes.

The interviewer must prepare a power point presentation for each case including histology (photographs of the slides or written findings) and photographs of the patients for all type of SCAR as well as the drawing for SJS/TEN. Make sure that there is neither any information on potential causes of SCAR nor the name of a patient on any sheet shown for review. Please check if the histology finding is readable, otherwise enlarge it.

SJS/TEN

The order for presentation is:

1. clinical sheet
2. drawing of affected skin (clearly differentiating between erythema and detachment)
3. histology
4. photographs

AGEP

Some questions on the clinical sheet can only be answered by the interviewer. Folds involvement means if the folds are actually involved or spared, no matter if the exanthema and/or pustules are widespread. For PNN it is important to count all PNNs. In some countries they are separated.

The order for presentation is:

1. photographs
2. histology
3. clinical sheet

HSS/DRESS

The interviewer has to check the clinical sheet and the flow chart.

The order for presentation is:

1. photographs
2. histology
3. clinical sheet
4. flowchart

For all cases after review

Only missing data or mistakes have to be completed/corrected. The interviewer has to inform the data center afterwards! If you receive additional information after a case review, which may be important, it can be entered into MACRO, but the case must then be reviewed again.

APPENDIX F
AGEP CASE REVIEW

Photo relevant: Shows anything that interfere with decision

Pustules:	**2**	Numerous (DOZENS = more than 24!) pin-head sized, non- follicular, can be confluent (not to be excluded)
	1	Pustules reported/seen, not scored as **2**, not suggestive of another disease
	0	Suggestive of another disease
Erythema	**2**	Slightly oedematous, homogenous in colour, livid reddish (not pink, nor purple), poorly demarcated
	1	Inhomogeneous
	0	Suggest something else: Ex dull, sharp demarcated = Psoriasis
Distribution	**2**	Accentuation of lesions (erythema / pustules) in the main folds
	1	Other distribution
	0	Localized (1 area)
Desquamation	**1**	Recognized as post pustular, with presence of small circular desquamative collerette
	0	Suggestive of another disease
Biopsy score	**3**	Sub-corneal Pustule, with spongiotic epidermis and dermal oedema
	2	Non specific pustule
	1	Exocytosis of neutrophils
	0	
	-10	Other disease = Excluded
Typical AGEP	**Yes**	With the pattern of clinical involvement re-enforced in the folds
	To be checked	
	No	Other type

Psoriasiform Histology Acanthosis, parakeratosis, dilatated vessels

For discussion

If pustule is clear (2 points), does post-pustular desquamation count as a point? NO
Definition of Resolution: means no more pustules and no more "active" erythema
Resolution $\leq$ 15 days, when unknown the score –4 is too strong. NO
Course Improve the wording in the sheet: Absence of erosive mucosal involvement **NO = -2 YES= 0**
Change of Time Frame for start of fever **3 days before onset + 1 day after onset (-3 to 1)**
Pustules on more than one site ←→Discussion of localized forms

Some clue for the interviewer

Do not confound erythema and distribution
Do not exclude purpuric/lichenoid papules, if present

APPENDIX G
HSS/DRESS CASE REVIEW

Criteria for rash suggesting HSS/DRESS

- scaling/desquamation
- facial edema
- purpura
- infiltration: at least 2 symptoms should be present to give 1 point (yes), otherwise 0/unknown, something that predicts something else -1 (no)

Liver involvement

- ALAT >2* upper normal limit on at least 2 successive dates **or**
- conjugated bilirubin >2* upper normal limit on at least 2 successive dates **or**
- ASAT, total bilirubin, alkaline phosphatase (AP) all >2* upper normal limit at least once

Lung involvement

- any evidence of interstitial involvement (X-ray, CT,...)
- abnormal BAL (lavage)
- abnormal blood gases
- cough is not enough

Kidney involvement

Creatinine level more than 1.5 times above the base level for the patient and/or proteinuria above 1g/d

Muscle/Heart

- raised CK
- Troponin T
- abnormalities in the ECHO
- weakness/pain is not enough

Pancreas

Amylase 2 or 3 times above normal

Serology

- hepatitis: at least 2 negative and 1 unknown => counted as negative
- mycoplasma/chlamydia: at least 1 negative and 1 unknown => counted as negative
- EBV/CMV: at least 1 negative and 1 unknown => counted as negative

If hepatitis and mycoplasma/chlamydia are negative but incomplete as described above and only one further negative result (either ANA or blood culture) is diagnosed => giving an extra point is an expert decision.

The serology score cannot be -1. I f a positive serology result is obtained the organ of involvement should be checked again during the review.

One bonus point should be given, if 3 negative serologies are obtained. This extra point is given independently of any other additional positive serology.

APPENDIX G
COMMON ADVICES
FOR DATA ENTRY IN MACRO

When an information cannot be observed, there are two variants to enter that correctly into MACRO.

1) If the information concerns an item where you can directly answer “unknown”, please tick the corresponding field.
   Example: page 5B, question concerning pustules, possible answers: “no”, “yes”, “unknown”.

2) If the information concerns an item where you cannot directly answer “unknown”, please mark the field as confirmed missing (enter “unobtainable”). Example: page 5B, question concerning quantity and kind of pustules, possible answers: only “yes” or “no”. So to avoid confusion, please mark the field as confirmed missing if you cannot answer.

Special characters and presentations

The MACRO system cannot handle special characters in a proper way. Therefore please avoid the usage of them. Only the usual (latin) alphabet, characters like “**.**”, “**,**”, ”+”, ”**-**“ etc. and numbers can be used.
Examples of character which should be avoided:
- Greek letters, eg. µg (please enter “microg” instead)
- apostrophes
- power of numbers, eg. 10^9 or 10^9 (please enter either full number or “10x9” or “10E9”)
- Special Characters like “~“ “|“ or “@“

If there is any question concerning the data entry please contact the data center
zks-regiscar@uniklinik-freiburg.de

ELECTRONIC FORM
RELEASE FOR VALIDATION
FOR ALL CASES AND CONTROLS

The "Release for validation" eForm is used in order to notify the data center that data validation (checks for completeness and plausibility of data) may start. This will prevent queries for incomplete or implausible data that might arise unnecessarily in cases where data entry is still ongoing.

Note: Whenever **corrections** to the data you entered become necessary, these can and should be done without any restriction **even after** you have **released the data for validation** by ticking "yes" on the variables listed below.

Item	**Description**
eForm (Case), Ready for validation, Group1 – Group 6	Mark "yes" when data entry is finished for the group of eForms indicated below.
eForm (Control), Ready for validation	Mark "yes" when data entry is finished for all control eForms.
X	should be completed
-	not applicable

eForm (Case)	**SJS/TEN**	**AGEP**	**HSS / DRESS**	
Patient's data	X	X	X	
Hospital data	X	X	X	
Diagnoses + clinical course	X	X	X	
Skin symptoms	X	X	X	
Pustules	-	X	-	Group 1
Mucosal symptoms	X	X	X	
Further information	X	X	X	
Organ involvement	-	-	X	
Adverse reactions on drugs	X	X	X	
Symptoms 1 month before SCAR 1	X	X	X	
Symptoms 1 month before SCAR 2	X	X	X	Group 2
Diseases in the past	X	X	X	
Medication history	X	X	X	
Discharge sheet	X	X	X	
Main Source of information	X	X	X	
Medical Imaging and Biopsies 1	-	-	X	
Medical Imaging and Biopsies 2	-	-	X	Group 3
Blood Cell Count	-	-	X	
Clinical Chemistry	-	-	X	
Laboratory Values 1	-	-	X	
Laboratory Values 2	-	-	X	
8 Week FU: General data	-	X	-	
8 Week FU: Pathologic findings	-	X	-	Group 4
8 Week FU: Additional remarks	-	X	-	

eForm (Case)	SJS/TEN	AGEP	HSS / DRESS	
Therapy 1	X	-	X	
Therapy 2	X	-	X	Group 5
Therapy 3	X	-	X	
1 Year Follow-up (all)	X	-	X	Group 6

eForm (Control)	Control	
Control 1: Demographic data	X	
Control 2: Diseases I	X	
Control 3: Diseases II	X	
Control 4: Adverse Reactions	X	

Data checks and queries

The Data Center will perform validation checks of the data entered in Macro on a regular basis using special validation programs.

-Which data are checked?

All data in Macro which are released for validation (see eForm "Release for Validation").
Depending on the review status / results the following data are checked:

Review status of patient	Data that will be checked
not finally reviewed	only page1-3 of 1st interview
excluded	only page1-3 of 1st interview
with possible diagnosis	complete 1st interview
with probable/definite diagnosis	complete 1st interview and follow up

Data are checked for discrepancies i.e. missing, implausible or inconsistent data.
Checks within a single eForm (page) are done as well as cross checks between data of different eForms (pages of questionnaires) holding related information.

- What happens when data are missing, an error/inconsistency is found?

ATTENTION:

Not all problems detected concern real mistakes but may reflect some exceptional/rare but real situation. For example: The age of patient entered in Macro is 110. In a case like that a discrepancy will only be detected because of extreme value.

The responsible interviewer/investigator has to clarify the discrepancies found by the validation checks.
For each abnormality the Data Center generates a single query sheet presenting the discrepancy.
(see Figure below)
All queries are pooled in a single word document.
The queries are sorted by interview number and according to the sequence of the corresponding paper forms.
The Data Center will send the word document via Email (password protected ZIP file) to the responsible investigator/interviewer and national supervisor(s) of the national center(s).
Additionally a table is attached listing all queries by interview number and query number to support handling of the queries.

-What information is listed on the query sheet:

Query number = a unique reference/identification number assigned to each query
Data extracted from Macro = date when the Macro data were extracted for validation, data entered up to this date are taken into account for validation
Interview = the interview number
Query = the question describing the discrepancy found by the validation check
eForm = Name of the corresponding eForm
No. = the number of the eForm, needed to identify repeating eForms, variables not in Macro but needed for the check
Data field = Name of the data field in Macro. "Kind of case" (= review status) and "Macro Subject ID" are listed on every query sheet
Data in Macro = value of the data field in Macro. All relevant data fields and their corresponding values are listed.
Attention: If needed for a better understanding of the query, supplementary (calculated) variables not found in Macro may be listed (e.g. kind of case, Minimum date of blisters/erosions). For these variables "eForm" and "Nr." is blank.

RegiSCAR Study Query number: 2153 Data extracted from Macro: 20.01.2009

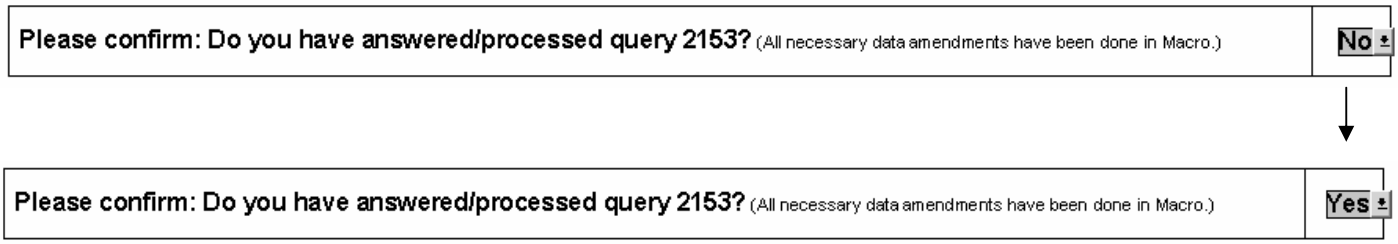
Interview	Query	eForm	Nr.	Data field	Data value in Macro
5150023	Please check data concerning headache		-	MACRO SUBJECT ID	14
			-	Kind of case	prob./def. HSS/DRESS
		Case HSS/DRESS p.6C2: Organ Involvement 2 (oh)	1	headache (OH)	-
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		
			-		

Please confirm: Do you have answered/processed query 2153? (All necessary data amendments have been done in Macro.) No

- What should be done by the national team?

The investigators/interviewers have to check each single query.
If a query asks to check a data item this normally means the value is either missing, out of range, inconsistent with other data or implausible.
Missing values should be completed or if the value is definitely not available marked as confirmed missing (=unobtainable). Make sure that all efforts were made to obtain the correct information before you mark the data as unobtainable.
Implausible, incorrect or inconsistent data must be amended in Macro.
If a value is correct no change in Macro is necessary.

If a query is finally resolved the last step should always be to confirm that the query is processed/answered. This is done by changing the value in the corresponding drop down menu on the query sheet from "No" to "Yes" (see Figure below).



If all queries are processed/resolved, the query word document should be returned to the Data Center.
At the Data Center the query tracking system will be updated accordingly.
The queries should only be returned to the Data Center, if they are finally and completely resolved (i.e. either data completed, corrected or confirmed).
Queries finally resolved but not returned to the Data Center will still be tracked as "still not finally resolved" and a reminder will be sent with the next batch of new queries.