KLH-21 version 3 Reporting adverse reactions to human medicinal products arising from clinical trials

This guideline supersedes guideline KLH-21 version 2 of September 1 2008 as of November 1 2008

This guideline defines the suspected serious unexpected adverse reactions reports (SUSARs) for medicinal products applied within the scope of conducted clinical trials which have been notified/authorised in compliance with Section 55, paragraphs 4 and 5 of Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended. The guideline is intended for sponsors, investigators, and persons cooperating therewith within the scope of clinical trials, and marketing authorisation holders, if they are involved in the conduct of clinical trials.
The purpose of urgent reporting of suspected serious unexpected adverse reactions is to provide new and essential information to the pharmacovigilance system of clinical trials ensuring a timely identification of signals which may imply a health risk to the involved subjects or which may imply a change to the safety profile of the investigational product (where the risk outweighs the potential benefit).
A properly working pharmacovigilance system allows for a further evaluation of serious signals and, where necessary, for the adoption of measures to minimise the risk associated with the use of investigational products presented to the enrolled trial subjects, including a timely provision of information to anybody involved (sponsors, investigators, included subjects, regulatory bodies, and members of ethics committees).
The guideline in a tabular format (Annex 1) defines the "reporting obligations" of anybody participating in the system, the scope and method thereof.

The requirements governing adverse reaction reporting are based upon the following:

- Act No 378/2007 Coll., on Pharmaceuticals and on Amendments to Some Related Acts (Act on Pharmaceuticals), as amended (hereinafter referred to as the Act);
- Relevant implementing regulations of this Act – Decree No 226/2008 Coll., on good clinical practice and detailed conditions of clinical trials of pharmaceuticals (hereinafter referred to as the Decree), and Decree No 228/2008 Coll., on marketing authorisation of medicinal products;
- International Conference on Harmonisation – E 6 – Good Clinical Practice: Consolidated Guideline published by EMEA as guideline CPMP/ICH/135/95;
- Guidance of the European Commission published in compliance with Directive 2001/20/EC (Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions /Eudravigilance – Clinical Trial Module/, Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – version 1, April 2004; Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – revision 2, April, 2006).

Abbreviations used:
SÚKL – State Institute for Drug Control
EC – Ethics Committee
MEC – Multicentric Ethics Committee
MP – Medicinal Product
IMP = Investigational Medicinal Product - shall mean a tested MP or comparator MP or placebo (please refer to the definitions provided in Section 51, paragraph 2(c) of the Act)
CT – clinical trial
IB – Investigator's Brochure
SPC – Summary of Product Characteristics
PhV - pharmacovigilance
GIT – gastrointestinal tract
MAH – Marketing Authorisation Holder
TS – trial subject
CRO – Contract Research Organisation

I. – DEFINITION OF TERMS USED IN PHARMACOVIGILANCE

Adverse event (abbreviated as AE) –shall mean an adverse change to the health affecting a patient or trial subject who is the recipient of a medicinal product, even if it is not known whether a causal relationship with the treatment by this product exists. (Section 3, paragraph 5 of the Act).

The term "adverse event" is a summary denomination of all situations which involve an adverse change to the health. It is used until it is possible to express at least a suspicion that the adverse change to health

could be caused by the administration of a specific medicinal product or products (incl. placebo). Because such suspicion cannot be expressed particularly where blinded clinical trials are concerned (the investigator does not know what product is taken by the patient) the term "adverse event" is by far the most used in the condition of clinical trials.

Adverse Drug Reaction (abbreviated as ADR) – shall mean an adverse and unintended response to the product administration which occurs at doses normally used for the prophylaxis, therapy or diagnosis of a disease or for the restoration, correction or other modification of physiological functions; where clinical trials on medicinal products are concerned, it shall mean an adverse and unintended reaction to any administered dose. (Section 3, paragraph 4 of the Act).

An adverse drug reaction is a term which implies a certain degree of causality. In a clinical trial it means an adverse event where a suspicion in respect of a causal relationship with a specific medicinal product or more products applied in the study may be expressed. In a blinded clinical trial it is possible to use the term "adverse drug reaction" only after the case is unblinded.

Serious Adverse Event (abbreviated as SAE) - shall mean such adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is demonstrated as a congenital anomaly or birth defect in offsprings, irrespective of the administered dose of the medicinal product (Section 3, paragraph 6 of the Act).

A serious adverse event is defined by the list of its consequences or symptoms which are explicitly considered serious.

Serious Adverse Drug Reaction (abbreviated as SADR) – shall mean such adverse drug reaction which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is demonstrated as a congenital anomaly or birth defect in offsprings, (Section 3, paragraph 4 (a) of the Act).

A serious adverse drug reaction is defined by the list of its consequences or symptoms which are explicitly considered serious. A restriction of capacities falls into the "significant incapacity or disability" group; in the enclosed translation of the CIOMS form it is the "serious restriction of activity - závažné omezení aktivity". Where, however, the restriction of capacities is not considered to be associated with the investigational medicinal product, it shall not be considered as an adverse reaction related to this product at all.

Unexpected Adverse Drug Reaction (abbreviated as UADR) - shall mean such adverse drug reaction the nature, severity or consequences of which are not consistent with the information laid down in the summary of the product characteristics for an authorised medicinal product or which are not consistent with available information, e.g. the investigator's brochure for an investigational medicinal product without marketing authorisation (Section 3, paragraph 4 (b) of the Act).

The unexpectedness is defined in particular by the inconsistency with data provided in the IB, Protocol or SPC. A mere fact that the concerned adverse reaction is or is not listed in the IB, Protocol or SPC hence shall not suffice for its determination. It shall involve an evaluation of an inconsistency with information provided in the IB, Protocol or SPC, in terms of the nature, severity, frequency of occurrence (rare vs. common) or consequence.

Example: If section 4.8 of the SPC contains the term "mild allergic reactions", an anaphylactic shock resulting in death may be identified as a serious and unexpected adverse drug reaction. Although the nature of the reaction is allergic, the severity and the consequence are inconsistent with the information provided in the SPC.

The expectedness or unexpectedness may be determined only for an adverse reaction. In the case of an adverse event the suspect product is not determined and therefore it is not possible to find out the information on the basis of which the unexpectedness could be determined.

Unexpected Serious Adverse Reactions – must comply with the definition of serious adverse drug reaction and, at the same time, that of an unexpected adverse drug reaction.

Suspected Unexpected Serious Adverse Reaction (abbreviated as **SUSAR)**

II. – LEGISLATIVE REQUIREMENTS GOVERNING REPORTING IN THE COURSE OF CLINICAL TRIALS

1. Obligations of the investigator

- The investigator shall be obliged to **forthwith** report to the **sponsor** all **serious adverse drug reactions** with the exception of those events which are defined in the Protocol or in the Investigator's Brochure as events not requiring immediate reporting (Section 58, paragraph 1 of the Act).
  Note: Forthwith shall mean no later than within 15 days of the moment when the investigator has learnt about the fact. This maximum period may be considered only in situations where the Protocol does not stipulate any shorter period.

Following the first initial report, additional information shall be provided in the follow-up report, if applicable. The report must include the identification of the trial subject (by the allocated identification code) and of the clinical trial (e.g. Protocol no., EudraCT number).

- In compliance with the requirements and in timelines stipulated by the Protocol the investigator shall report to the **sponsor adverse events** and **critical laboratory deviations** (Section 58, paragraph 1 of the Act; Section 10, paragraph 2 of the Decree).

- In the case of a death of a trial subject, the investigator shall be obliged to provide the required additional information to the sponsor and to the Ethics Committee (MEC and the concerned local EC) (Section 58, paragraph 2 of the Act).

2. Obligations of the sponsor

The sponsor shall be fully responsible for the conduct of the clinical trial and for the **safety of the involved trial subjects**. The following obligations of the sponsor are associated with the aim to safeguard the safety of trial subjects:

- The sponsor shall be obliged to ensure that any information about **suspected serious unexpected adverse drug reactions (SUSARs)** resulting in **death** or **life-threatening for the trial subject,** are recorded and reported to **SÚKL** and to concerned **Ethics Committees without any delay, no later, however, than within 7 days** of the day when the sponsor has learnt about this fact and that any subsequent additional information, if necessary, is forwarded within the next **8 days** (Section 58, paragraph 4 of the Act). Where all of the necessary information is contained in the initial report, it is not necessary to provide a follow-up report.
- In the case of other suspected **serious unexpected adverse drug reactions** the sponsor shall ensure that a report thereof is provided to **SÚKL** and to the concerned **Ethics Committees** no later than **within 15 days** of the day when the sponsor has learnt about this fact (Section 58, paragraph 5 of the Act).
  Note:
  *- reports arising from blinded clinical trials **MUST BE UNBLINDED;***
  - the concerned ECs shall, in the case of a multicentric clinical trial, mean the MEC which has issued its approval of the CT conduct, and in the below listed cases also the local ECs for the sites where the CT in question is being conducted;
  - in the case of electronic reports, the sponsor shall report to the EudraVigilance database; where SUSARs occurring within the territory of the Czech Republic are concerned, reports shall be provided to the EudraVigilance database as well as to SÚKL (Sender's Comments); in any other cases, reports shall be sent only to the EU database.
- The sponsor shall inform the investigators of any **suspected unexpected serious adverse drug reactions** to the IMP reported thereto (Section 58, paragraph 7 of the Act; Section 12, paragraph 12 (d) of the Decree).
- The sponsor shall maintain detailed records of all adverse events reported thereto by the investigator(s). Upon request the sponsor shall provide these records to SÚKL (Section 58, paragraph 3 of the Act); the sponsor shall, moreover, provide these records upon request to the competent authorities of the Member States on whose territory the clinical trial is also active (Section 58, paragraph 3 of the Act).
- The sponsor shall, on an annual basis or upon request, submit to SÚKL and to the Ethics Committee (to the MEC where multicentric CTs are concerned, or to the EC which has approved the trial in the case of mono-centric CTs) the **Annual Safety Report**, which reflects any new information which is available and which has been obtained during the period which the report pertains to. This report shall be identical for SÚKL as well as for the EC (the MEC where multicentric CTs are concerned, or

the EC which has approved the trial in the case of mono-centric CTs) (the contents shall follow the syllabus provided in Annex 7 of the Decree). The submission of this report is based upon the requirements set forth in the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" and on the effective legislation (Section 58, paragraph 8 of the Act; Section 15, paragraph 4 of the Decree). With respect to the mentioned document, this report does not have to be submitted in the interval of one year of the notification/authorisation of the concerned clinical trial in the Czech Republic. The interval of its submission shall be derived from the commencement of the clinical trial in the Community and may change in the course of the clinical trial, if the tested medicinal product is authorised. Then the interval may be related to the International Birth Date (IBD).

- In the course of the clinical trial, the sponsor shall provide to SÚKL and to the Ethics Committee (to the MEC where multicentric CTs are concerned, or to the EC which has approved the trial in the case of mono-centric CTs) **the Annual Report** on the conduct of the clinical trial every 12 months, no later than within 60 days of the end of this period (the start of this period shall be related to the commencement of the CT in the Czech Republic) (Section 58, paragraph 8 of the Act; Section 15, paragraph 3 of the Decree) within the scope set forth in Annex 6 of the Decree.
  Notes:
  ASRs should not be sent to SÚKL after the approval of the clinical trial and before its commencement; *SUSAR reports from abroad should only be made electronically to the EudraVigilance database, where the sponsor does not report electronically, SUSAR reports from abroad should not be sent to SÚKL. The reporting obligation will commence as of the commencement of the CT in the Czech Republic.*

Information sent to SÚKL, concerned Ethics Committee and investigators involved in the given clinical trial if the clinical trial is suspended or terminated in the Czech Republic:
*Where the conduct of the clinical trial is suspended in the Czech Republic, A**nnual Safety Reports** should be sent in compliance with the original timelines.*
In the case of a terminated clinical trial in the Czech Republic the sponsor should forthwith provide the information, where unexpected safety information is concerned, it should be accompanied by proposed measures to be adopted, if the information significantly alters the risk-benefit ratio and may affect trial subjects involved in the terminated trial. After the clinical trial is terminated in the Czech Republic, the Annual Safety Reports should no longer be submitted, even if the clinical trial continues abroad.

III. – RECORDING, EVALUATION AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS

The sponsor shall be responsible for the establishment of a system for the reporting, evaluation, and collection of data and for the reporting of AEs and ADRs of all types by drafting standard operating procedures which have to be executed in writing.
The sponsor should evaluate the records of all **adverse events** in terms of their severity and causality *(in compliance with the above provided definitions).*
Any **adverse events** rated by the investigator or the sponsor as suspect of causality with the investigational medicinal product will be classified as **adverse reactions.** The evaluation of causality by the investigator must not be disputed by the sponsor; where the sponsor does not agree with the investigator in the issue of causality evaluation both opinions have to be specified in the report.
The expectedness of reactions must be defined by the sponsor in the Protocol, IB or SPC with a view to available information about the product. Where various SPCs of the same investigational MP exist in various countries, the sponsor shall choose one SPC (specified in the Protocol) as the reference one and expectedness shall be established on the basis thereof. When **unexpectedness of an adverse reaction** is evaluated, it will mean the evaluation of inconsistency with the information provided in the IB, Protocol or SPC in respect of the nature, severity and frequency of occurrence (rare vs. common), or consequence (*see the definition of UADR above*).

1) WHO HAS TO REPORT WHAT AND TO WHOM

To SÚKL – reported by **sponsor**

- Only reports on **SUSARs,** i.e. suspect cases derived from **unblinded** data

FORTHWITH

- **SUSARs of the IMP** (with or without marketing authorisation in the Czech Republic) arising from the concerned clinical trial and occurring within the territory of the Czech Republic, which result in death or are life-threatening for trial subjects: within 7 days + follow-up report within the next 8 days

(where all information was provided in the initial report, the follow-up report shall not be sent again); other SUSARs from the Czech Republic within 15 days

*- for **MPs with and without marketing authorisation in the Czech Republic** reports will be submitted to SÚKL Clinical Trials dept.*

- **SUSARs of the IMP** (with or without marketing authorisation in the Czech Republic) arising from the concerned clinical trial conducted within the territory of the Czech Republic, which have occurred abroad (within the territory of the EU or in a third country) and which result in death: within 7 days + follow-up report within the next 8 days (where all information was provided in the initial report, the follow-up report will not be sent again); other SUSARs within 15 days;

  - if the sponsor reports electronically to the EudraVigilance database, the obligation to report to SÚKL is met thereby (separate reports should not be sent to SÚKL), in the case of other than electronic reporting (e.g. CIOMS) reports should be submitted to the Clinical Trials dept.

  Additional remark:

  ***A SUSAR of a tested MP** (with or without marketing authorisation in the EU) arising from another clinical trial and occurring in the Czech Republic or within the territory of the EU or in a third country will not be reported separately where a CT on the identical tested product is concerned;* reporting will be made to the EudraVigilance database.
- Any changes increasing the risk for trial subjects and new information which may adversely affect the safety of trial subjects or the conduct of the clinical trial will be reported immediately, within timelines reflecting the expected degree of significance of the information and risk for patients.

OTHER REPORTING

- **Annual Safety Reports** – the sponsor shall submit the Annual Safety Report which reflects any newly available information obtained in the course of the period which the report pertains to once a year. The contents of the report shall be governed by *Annex 7 of the Decree;* reports are required to be sent only electronically.
- **SUSARs obtained from spontaneous reports or from literature –** these should be reported by the sponsor in the Annual Safety Report or, where necessary, sooner as an extraordinary safety report.
- **Updated version of the IB –** at least once a year (Section 56, paragraph 4 of the Act).
- **Line listing – version for the EC – only upon request**

To the EC – reported by **sponsor**

- Only reports on **SUSARs,** i.e. suspect cases derived from **unblinded** data

FORTHWITH

- **SUSARs of the IMP** (with or without marketing authorisation) arising from the concerned clinical trial and occurring within the territory of the Czech Republic, which result in death or are life-threatening for trial subjects: within 7 days + follow-up report within the next 8 days (where all information was provided in the initial report, the follow-up report will not be sent again); other SUSARs from the Czech Republic should be reported within 15 days. The sponsor will inform the MEC and the local EC for the site where the SUSAR has occurred.

  *Note: The sponsor should send individual reports to the **Ethics Committees**, if possible, upon the follow-up, amended by a brief description of the expected causality and specifying necessary measures, or a rationale explaining why no measure is needed, as applicable.*
- The sponsor should forthwith report about any changes increasing the risk for trial subjects and new information which may adversely affect the safety of trial subjects or the conduct of the clinical trial, incl. SUSAR reports classified as mentioned above from abroad.

OTHER REPORTING

- **"Line listing"** together with a cover letter which includes the evaluation of the safety situation, whether it is necessary to adopt safety measures, and if so, which ones, incl. their justification. Line listing contains SUSAR reports for the IMP (authorised in the Czech Republic as well as non-authorised in the Czech Republic) arising from the concerned clinical trial conducted within the territory of the Czech Republic which have occurred abroad (within the territory of the EU or in a third country). It should be sent by the sponsor every six months, only to the MEC. Line listing should be sent within the period of 30 days of the date of data collection completion for the given period.
- **Annual Safety Reports** – the sponsor should submit the Annual Safety Report which reflects any newly available information obtained in the course of the period which the report pertains to once a year. The contents of the report have to be governed by *Annex 7 of the Decree. The timelines for submission are identical to those for the Annual Report submission to SÚKL (see above).* To be sent only electronically.

- **SUSARs obtained from spontaneous reports or from literature –** these will be reported by the sponsor in the Annual Safety Report or, where necessary, sooner as an extraordinary safety report.
  Note: The sponsor should not report any other SUSARs to the EC.

TO INVESTIGATORS – reported by the **sponsor**

- The sponsor should report **SUSARs**, i.e. suspect cases derived from unblinded data, but without subject identification (i.e. without the identification of code of the trial subject), and without information about the medicinal product and/or blinded reports.

- **SUSARs** of the investigational MP (with or without marketing authorisation in the Czech Republic) arising from the concerned clinical trial and occurring within the territory of the Czech Republic: within 15 days, but without subject identifier – without complete subject identification and without identification of the medicinal product.
- **SUSARs** of the investigational MP (with or without marketing authorisation in the Czech Republic) arising from the concerned clinical trial and occurring within the territory of the EU or in a third country either within 15 days; unblinded, but without subject identifier – without complete subject identification and without identification of the medicinal product or in "line listings" every six months; without subject identifier – without complete subject identification and without identification of the medicinal product
- **"Line listing"** – of SUSARs of the tested MP (with or without marketing authorisation in the EU) arising from another clinical trial on the same tested MP conducted within the territory of the Czech Republic, which have occurred within the territory of the Czech Republic or of SUSARs arising from another clinical trial on the same tested MP conducted within the territory of the Czech Republic, which have occurred within the territory of the EU or in a third country. It will be sent by the sponsor every six months without giving the identification codes of subjects and without the identification of the MP.

2) WHAT SHOULD NOT BE REPORTED

- serious, but expected reactions;
- non-serious reactions, irrespective of their expectedness;
- events evaluated as being without causality with the IMP;
- *blinded reports shall not be sent. !!!*

3) RECOMMENDATIONS FOR UNBLINDING

The major rule for SUSAR reporting to SÚKL and the ECs is unblinding before report submission. As it is, however, desirable to maintain blinding for all patients prior to the final analysis, it is recommended that the sponsor only unblinds the particular patient. The sponsor should strive to opt for such method of monitoring and processing of safety data which allows for maintaining the blinding for persons responsible for data analysis and interpretation of results in study conclusions. The unblinding of individual cases by investigators in the course of the study should be conducted exclusively with respect to the subject safety – only in exceptional emergencies and in compliance with the Protocol.
Where a blinded study is concerned, it is recommended to assess the severity, expectedness and possible causal relationship of the SADR/SAE with the investigational MP in terms of its potential effects. If, after such assessment, the case appears to be a SUSAR, unblinding is necessary. In this case it is necessary to reconsider, before reporting, the expectedness and the method of reporting implied thereby in respect of the specific product (tested, comparator including placebo vs. authorised, non-authorised vs. information from the Protocol, IB, SPC).
In clinical trials studying high mortality and/or morbidity conditions where the endpoints of the evaluation of efficacy may be fatal or serious conditions, unblinding would compromise the integrity of the study. That is why it is recommended to include in the Protocol of such special cases a modification of USAR reporting so that serious conditions which may be considered related to the disease would not have to be reported through the system of immediate unblinding of reports. SÚKL will approve such modification within the scope of assessment and approval of the Protocol of the concerned CT. If an USAR which does not represent an endpoint arises, it has to be reported in the usual manner. Sponsors are, moreover, advised to establish an independent data monitoring committee (IDMC) which would evaluate data in present intervals and on grounds of the results of safety analysis could advise the sponsor whether it is possible to continue the CT without modifications, whether measures or changes should be adopted or whether the study should be terminated.

4) REPORTING FORMATS

The sponsor should send to **SÚKL** reports in electronic format (to the ID for electronic reporting CZSUKL) in the format stipulated by the recommendation **ENTR-6101** *Detailed Guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance-Clinical Trial Module) by specifying SÚKL as a co-addressee.*
If the sponsor has reported SUSARs to SÚKL on the CIOMS forms, he/she should be aware that the obligation to submit these reports retrospectively from **May 1 2004** to the Eudravigilance database is still effective; the SÚKL CDNÚ database does not require retrospective reporting. This obligation will not be applicable to sponsors not supported by pharmaceutical companies, i.e. grant studies submitted by medical doctors or by professional societies.
In the case of electronic reporting, the EudraCT number has to be entered at the start of the A.2.3.1 item and separated from the company name proper with the # symbol.

If the reports are not sent electronically as laid down in the PHV- 4 guideline, they should be sent only via e-mail to: klinsekret@sukl.cz

Archival formats zip and rar may be used for the sending of reports. For safety reasons SÚKL will not accept self-opening archives of the exe or similar formats.
Other safety information subjected to immediate reporting should be notified by means of a letter as reports pertaining to safety, specifying the EudraCT number, Protocol number and, if applicable, file number/SÚKL identifier for the study concerned. The letter should include brief information about the problem and proposed solution or a description specifying how the sponsor intends to proceed in solving the issue.

The format of electronic reporting is further detailed in guideline PHV-4.

5) MINIMUM CONTENT OF THE REPORT

a) Serious adverse drug reaction report by the investigator to the sponsor should contain at least the following data (Section 10, paragraph 1 of the Decree)**:**

- Information about trial site;
- Name of the sponsor;
- Name of the clinical trial and Protocol number;
- Patient identification;
- Description of the event;
- Names of all medicinal products taken by the subject, incl. the administered dose and method of administration;
- Evaluation of causality between the AE and the investigational MP.

Note: The above-mentioned requirements reflect the minimum particulars of reporting, nevertheless, to be able to properly assess causality, it is advisable to provide other relevant information, e.g. concomitant treatment with other medicinal products or various dietary supplements, which might be involved in the event. Detailed specification of contents and method of reporting should form part of the Protocol of any study. The name of the medicinal product may be replaced with the name of the active substance or the code of the pharmaceutical.

b) A suspected serious unexpected adverse reaction report by the sponsor should contain at least the following:

- Name of the sponsor;
- Name of the clinical trial and Protocol number, EudraCT (if allocated) or other code for easier traceability (e.g. SÚKL identification code or file no.);
- Identification of the source of reporting (trial site); not to be specified if reported by the investigator;
- Patient identification *(Note: any identification, e.g. by a code, shall be considered sufficient);* not to be specified if reported by the investigator;
- Description of the adverse reaction *(Note: using MedDRA terminology);*
- Name of the medicinal product causing the adverse reaction, incl. the administered dose and method of administration, not to be specified if reported by the investigator;
- Evaluation of causality between the adverse reaction and the administration of the medicinal product.

c) Line listing (a list) should bear an identification number, date and time of compilation and should **include** the following information about each SUSAR, in particular**:**

- Identification of the clinical trial (Protocol number or EudraCT number);
- Identification number of the trial subject in the study *(not to be specified if reported by the investigator);*
- Case-ID-Number in the sponsor's database;

- Country of origin of the case;
- Age and gender of the trial subject;
- Daily dose of the investigational medicinal product (and pharmaceutical form and method of administration, if possible); not to be specified if reported by the investigator;
- Date of onset of the AR (if not available, then an estimate based on treatment commencement);
- Duration of treatment (if not available, then an estimate thereof);
- Description of the adverse reaction (signs, symptoms, in the MeDRA terminology, if practicable);
- Evaluation of the final condition of the patient (e.g. improved, recovered, fatal, with consequences, etc.);
- Evaluation of causality (if investigator's and sponsor's evaluations are diverging, both shall be provided) and of expectedness.

ANNEXES

Annex 1 – Pharmacovigilance reporting from clinical trials tabular overview

PHARMACOVIGILANCE REPORTING FROM CLINICAL TRIALS TABULAR OVERVIEW

SUSAR – from a CT which is conducted within the territory of the Czech Republic – the sponsor should report: SUSARs for IMP (tested and comparators, incl. placebo, if applicable)		
	MP AUTHORISED in the Czech Republic	MP NON-AUTHORISED in the Czech Republic
Reports from the Czech Republic	system A (to CT)	system A (to CT)
Reports from abroad – EU or third countries	system B	system B
SUSAR – another CT, but identical tested MP – the sponsor shall report: SUSARs for **tested MP**; reports for comparator MP are not required **(as these may differ in various CTs).**		
	AUTHORISED in the EU ***(this includes also marketing authorisation in the Czech Republic)***	NON-AUTHORISED in the EU
Reports from the Czech Republic	system C	system C
Reports from abroad – EU or third countries	system D	system E
Spontaneous reports and/or literature	system F	system F

If the sponsor is not the MAH, he/she has to report SUSARs for authorised investigational medicinal products from the CT and report them also to the MAH; individual unblinded SUSARs shall be reported.

A)
To **SÚKL** (in electronic format to the CDNÚ or in writing by e-mail to the CT dept.) – only unblinded; those that result in death or are life-threatening: 7+ 8 days, others within 15 days;
- concurrent ongoing monitoring and evaluation should be carried out; if safety measures are found to be necessary, SÚKL has to be informed immediately (to the effect that measures are necessary, which ones, and why).

To the concerned ECs (MEC and **LEC** of the site where the SUSAR has occurred)
only unblinded; those that result in death or are life-threatening: 7+ 8 days, others within 15 days;
- if safety measures are found to be necessary, MEC has to be informed immediately (to the effect that measures are necessary, which ones, and why).

To other investigators involved in the concerned CT
- blinded or unblinded, but without the identification code of the trial subject and without the specification of the MP, no later than within 15 days;
- if safety measures are found to be necessary, all investigators have to be informed immediately (to the effect that measures are necessary, which ones, and why).

B)
To **SÚKL** (CT dept.)
- *if the sponsor reports electronically to the EudraVigilance database, this fulfils the obligation to report to SÚKL (separate reports to SÚKL should not be sent);*
- where the reporting is not electronic, only unblinded reports should be sent; those that result in death or are life-threatening: 7+ 8 days, others within 15 days;
- concurrent ongoing monitoring and evaluation should be carried out, if safety measures are found to be necessary, SÚKL has to be informed immediately (to the effect that measures are necessary, which ones, and why);
- "Line listing"+ cover letter containing the evaluation of the safety situation by the sponsor (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why) only upon SÚKL's request.

To the concerned MEC

- every six months – by means of “Line listing“ + cover letter containing the evaluation of the safety situation by the sponsor (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why);
- if safety measures are found to be necessary, MEC has to be informed within 15 days at the latest (to the effect that measures are necessary, which ones, and why).

To other investigators involved in the concerned CT
- blinded or unblinded, but without the identification code of the trial subject and without the specification of the MP, no later than within 15 days or in “line listing” every six months- according to sponsor reporting system
- if safety measures are found to be necessary, all investigators have to be informed immediately (to the effect that measures are necessary, which ones, and why).

C)

To **SÚKL** (CT dept.) – not necessary, reported for the original CT – for the original CT only add the identification of all CTs with the same tested MP; where electronic reporting is concerned, provide this information in “**Sender’s Comments”;**
- if safety measures are found to be necessary, immediately, no later than within 15 days (to the effect that measures are necessary, which ones, and why)

To the concerned MEC
- individual reports should not be notified;
- if safety measures are found to be necessary, MEC has to be informed immediately (to the effect that measures are necessary, which ones, and why).

To other investigators involved in the concerned CT
- every six months – by means of “Line listing“ – evaluation of SUSAR with the same product), but without identification of code of the trial subject and of the medicinal product + cover letter containing the evaluation of the safety situation by the sponsor (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why);
- if safety measures are found to be necessary, all investigators have to be informed immediately (to the effect that measures are necessary, which ones, and why).

D)

To **SÚKL**
- individual reports are not necessary, they are in the EudraVigilance database (if, during the entering of data in the database the entries are evaluated as a signal triggering an action – it will be implemented within Europe /*Pharmacovigilance Working Party PhVWP/)*;
- only if these reports are evaluated by the sponsor as a signal triggering a safety measure – sponsor should send the data as a new information on the product safety incl. proposed measures; in this case the sponsor will inform SÚKL forthwith following the evaluation of such situation.

To the concerned MEC – individual reports should not be sent, these shall be provided within the evaluation by means of the “Annual Safety Report“ at least once a year **or** if necessary, sooner as an extraordinary safety report – processed and evaluated (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why).

To other investigators involved in the concerned CT
- every six months – by means of “Line listing“ (without TS and MP identification); this line listing will contain all SUSARs from the relevant trials (i.e. trials on the same medicinal product) + cover letter containing the evaluation of the safety situation by the sponsor (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why);
- if safety measures are found to be necessary, all investigators have to be informed immediately (to the effect that measures are necessary, which ones, and why).

E)

To **SÚKL**
- *if the sponsor reports electronically to the EudraVigilance database, this fulfils the obligation to report to SÚKL; separate reports to SÚKL shall not be sent;*

To the concerned MEC – individual reports should not be sent, these should be provided as part of the “Annual Safety Report“ at least once a year **or** if necessary, sooner as an extraordinary safety report – processed and evaluated (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why).

To other investigators involved in the concerned CT
- every six months – by means of "Line listing" (without trial subject and MP identification); this line listing will contain all SUSARs from the relevant trials (i.e. trials on the same medicinal product) + cover letter containing the evaluation of the safety situation by the sponsor (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why);
- if safety measures are found to be necessary, inform immediately (to the effect that measures are necessary, which ones, and why).

F)
To **SÚKL (CT dept.**), to the **concerned ECs**, to **other investigators**: individual reports should not be sent (reasoning: spontaneous report and/or literature report should be completed in ASR) **or** if necessary, sooner as an extraordinary safety report – processed and evaluated (whether it is necessary to adopt measures and which ones, or whether measures are not necessary and why).