SINDUSFARMA and ABRACRO Clinical Research and Pharmacovigilance Working Groups

Understanding and application of Circular Letter Nº 13/2020-CONEP/SECNS/MS

1 – INTRODUCTION

Clarification and adequacy proposals as per Circular Letter No. 13/2020-CONEP/SECNS/MS described herein provide a joint action between SINDUSFARMA and ABRACRO with the representation of regulatory affairs, clinical operations, and pharmacovigilance areas after alignment meetings with the Brazilian National Research Ethics Committee (CONEP). This document content aims to clarify, guide and propose harmonization, helping Clinical Researches Sites and Sponsors in the process steps of preparing and submitting to Ethics Committees (CEPs) the requirements of the Circular Letter No. 13/2020-CONEP/SECNS/MS

After three years of preparation by CONEP, the Circular Letter No. 13/2020-CONEP/SECNS/MS that provides for the transmission of Adverse Events via CEP/CONEP System was published on June 02, 2020, therefore revoking Circular Letter No. 008/2011-CONEP/SECNS/MS.

After some discussions with clinical operations and pharmacovigilance work groups, several questions were raised, concerning concepts, requests, workflows and scope of Circular Letter No. 13/2020; and in order to clarify and alignment the members understanding meetings were hold with CONEP on September 17 and 23, 2020.

2 – GENERAL CONSIDERATIONS

Circular Letter No. 13/2020 - CONEP/SECNS/MS provides for the transmission of adverse events in the CEP/CONEP System, being the clinical research site in charge of the reports elaboration and submission via Brazil Platform. Therefore, it is understood that sites have autonomy for preparing their respective notifications of adverse event to CEPs both in tabular form and as Consolidated Report, such as the communication autonomy between the coordinator site and the participants sites.

On the other hand, the sponsor will support the investigator clinical research site with additional guidelines and information required, in order to make it feasible that the site to fulfill with the Circular Letter No.13/2020-CONEP/SECNS/MS requirements.

3 – DISCUSSION

Items mentioned below reflect alignment carried out during meetings with CONEP.

3.1 - SERIOUS ADVERSE EVENT (SAE) concepts

Initially, it is noted that there is no item in the Circular Letter No. 13/2020-CONEP/SECNS/MS that mentions the SAEs coverage for notification; however, it was informed by CONEP that adverse events concerning only the study at issue shall be notified both for the ones occurring in Brazil and international ones.

Definition of item 3.4 SERIOUS ADVERSE EVENT (SAE) in this letter differs from the current definition in Anvisa regulation as shown below:

> **Serious Adverse Event as per Circular Letter No. 13/2020** is any unfavorable occurrence with the clinical trial participant, after signing the ICF, which results in: 1) Death; 2) Threat or risk of life; 3) require of hospitalization; 4) Extension of pre-existing hospitalization; 5) disability or permanent damage; 6) Congenital anomaly; or 7) Significant medical occurrence that, based on appropriate medical opinion, may injure the participant and/or require medical or surgical intervention to avoid any other occurrences mentioned. Synonym: serious adverse event.
>
> **Serious Adverse Event as per RDC no. 09/2015** is the one that results in any adverse experience with medications, biological products or devices, occurring in any dose and that results in any of the following outcomes: a) death; b) life threatening; c) persistent or significant disability / invalidity; d) demands hospitalization or extended admission; e) congenital anomaly or birth defect; f) any suspicious transmission of infectious agent through medicine or; g) clinically significant event.

Despite the difference shown above, there will be no need to adequate of Circular Letter No. 13/2020-CONEP/SECNS/MS to align the seriousness criteria terms between ANVISA and CONEP. As aligned in this meeting, in case of seriousness criteria occurrence “f) any suspicion of infectious agent transmission by means of medicine”, it can be described as “Significant medical occurrence”.

3.2 – Guidelines to fill out adverse event tables

The **index adverse event (3.5)** is the one that corresponds to initial adverse event occurred with the participant, that can have full resolution or causes a **further adverse event (3.6)** that occurs sequentially and due to previous one.

In case investigator assessment is not clear the categorization as index adverse event or further adverse event, can be rated as index adverse event. However, it is important that events are grouped per participant taking into consideration time relation, in order to enable assessment by CEP/CONEP System.

To fill out item 4.3.2 VII - Causality with investigational product or research procedure ("non-related", "possibly related", "probably related", "definitely related"), can be filled in as reported in site file / participant CRF. In other words, if the options to assess causality are only "related" or "non-related", such terms can be used in the table.

To fill out item 4.3.2 X - Participant situation in the last updating date ("in progress", "recovered without sequels", "recovered with sequels" and "death"), CONEP understands that the situation shall be filled as per the general clinical status of the participant and not per event. I.e., in case the participant has recovered from an event, but is still recovering from another one, it shall be informed "in progress" for both. CONEP understanding is that participant general clinical status assessment prevails. In case investigator considers relevant, evolution/outcome of each even can be added.

As per item 4.3.2 XI Description of research participants discontinuity, such information can be inserted in the last column of template table (refer to topic - 4. Table Templates, form and Report), taking into consideration that the item has not been included in the template table submitted by Circular Letter No. 13/2020-CONEP/SECNS/MS.

3.3 – Adverse Events Table submission frequency

As there is no determination of frequency for Adverse Event Table submission, it is the investigator discretion / site SOP (Standard Operational Procedure) that defines it or submit as per CEP guidelines.

3.4 – Consolidated Report of each site

It was suggested to CONEP that for item 4.6 I - SAE absolute and relative distribution; the suggestion to include information about **event related x event non-related** and aligned to the understanding on how the report can be presented.

Relative distribution rate shall be based on the amount of the participants in the clinical trial. Example as follows:

SAEs absolute distribution[1]	**20**
Quantity of participants in the research	**100**

SAEs relative distribution

Types of SAEs[2]	Related		Non-related		Total	
	Absolute value	Relative rate	Absolute value	Relative rate	Absolute value	Relative rate
Death	**0**	**0%**	**1**	**1%**	**1**	**1%**
Threat or risk of life	**0**	**0%**	**0**	**0**	**0**	**0**
Need of hospitalization / Extension of pre-existent hospitalization	**3**	**3%**	**2**	**2%**	**5**	**5%**
Disability or permanent damage	**0**	**0%**	**0**	**0**	**0**	**0**
Congenital anomaly	**0**	**0%**	**0**	**0**	**0**	**0**
Significant medical occurrence	**6**	**6%**	**8**	**8%**	**14**	**14%**
Total	**9**	**9%**	**11**	**11%**	**20**	**20%**

For item 4.6 II - Detailed description of cases in which there is sequel and death due to participation in the research), for description of cases where there is sequel can be considered “Disability or permanent damage” seriousness criteria.

As per the detailed description, CONEP has informed that it is the investigator´s discretion; however, no extensive descriptions shall be forwarded nor in line listing format.

3.5 – Consolidated Report – including information from all sites

For item 4.7, in case of multicenter trials, investigator from site related to coordinating CEP, additionally, shall prepare a consolidated report containing the adverse events information of all clinical trial sites and submit it to CEP to which it is related, via Brazil Platform, using “notification” functionality, at the time of partial and final trial reports submission.

It was aligned with CONEP that, due to the impossibility of the coordinator site to access the information from participant sites through the Brazil Platform, the Consolidated Reports from other participant sites need to be shared by other mechanism, such as via e-mail, attending the criteria of safety, secrecy and confidentiality for the participants and the study.

Besides, currently, sites have different submission timelines, to facilitate and harmonize the elaboration of consolidated partial report of all sites, these can be submitted taking into consideration the coordinator site submission timelines - in case of multicenter studies.

Example of the submission timelines difference:

Example of cenario for Partial and Final Report Submission

Coordinator Site:

09/Sep/2020

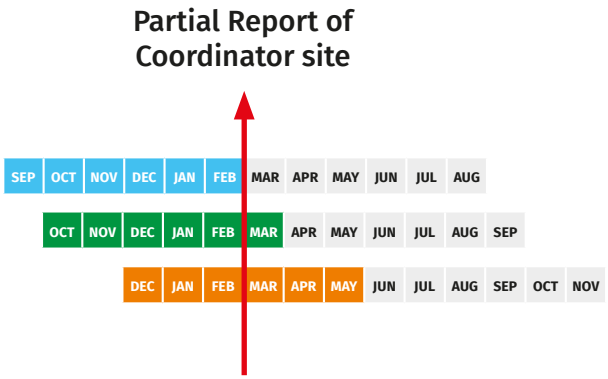
Consider the local EC coordinator/CONEP approval

Site 2:

15/Oct/2020

Site 3:

30/Dec/2020



3.6 – Consolidated report – International Adverse Events

For international adverse events, related to item 5. Processing international adverse events, only SUSARs will be notified as per the specific trial, and information will be submitted in the Consolidated report format as requested in Circular Letter No.13/2020-CONEP/SECNS/MS.

Adverse events assessed as SUSAR (Suspected Unexpected Serious Adverse Reaction) are serious events, related to the product under investigation and unexpected, i.e., they are not described in the investigator brochure or leaflet. Such types of events have information processed and assessed as per causality and expectedness that help in evaluating participant´s safety.

In item 5.3. I - Absolute and relative distribution of SAE, will only be accounted for SUSARs for the adverse events occurred internationally. The table will have absolute and relative accounting of serious events, related and unexpected, as per the example below:

SAEs absolute distribution[1]	**9**
Quantity of participants in the research	**100**

SAEs relative distribution

Types of SAEs[2]	Total of serious events, related and unexpected[4]	
	Absolute Value	Relative Value
Death	**0**	**0%**
Threat or risk of life	**0**	**0%**
Need of hospitalization / Extension of pre-existent hospitalization	**3**	**3%**
Disability or permanent damage	**0**	**0%**
Congenital anomaly	**0**	**0%**
Significant medical occurrence	**6**	**6%**
Total[3]	**9**	**9%**

For item 5.3 II - Detailed description of cases in which there is sequel or death due to the participation in the research (and not for disease progression), translation of narrative contained in CIOMS form of SUSAR can be forwarded; given that CIOMS document must not be attached to the consolidated report, following the provision of item 5.4. Individual notification standard-form submission as "CIOMS", "FDA/Medwatch", among others will not be accepted as consolidated report.

According to item 5.2. the consolidated report should be submitted via CEP/CONEP system to CEP related to coordinating site, at any time, using "notification" function; additionally, according to item 5.6. Coordinator sites are responsible for forwarding consolidated reports to the participant and co-participant sites. In other words, the Circular Letter No. 13/2020 establishes that the investigator from coordinating site is responsible for the submission of consolidate report to respective CEP and its distribution to participant sites; however, it does not state about the submission of the consolidate report to CEPs related to those participant sites. Considering item 5 of Resolution 346/2005, - "Only the CEP of the first site will be in charge of the notifications to CONEP in case serious adverse events occurred in foreign sites, clinical trial discontinuations or relevant changes, keeping the necessary notifications of each investigator to the local CEP", the submission of consolidated report from all participant sites to their respective CEPs can be according to investigator´s/site SOP discretion or as determined by the CEP ("required CEP necessary notifications");

3.7 – Adequacy deadline

Adequacy to Circular Letter No.13/2020 was in force since the release date (June 2nd, 2020), however, after SINDUSFARMA and ABRACO request, extension to 180 days term was granted by CONEP, which was formalized by Circular Letter 17/2020, released on October 08, 2020, determining, therefore, the date of December 05, 2020 for adequacy of Circular Letter No.13/2020-CONEP/SECNS/MS.

4 – TABLE AND REPORTS TEMPLATES

Considering the discussion in the meetings and what is presented above, the group suggests the table and reports templates to be submitted to CEP/CONEP system.

4.1 – Table Template of SAEs occurred in Brazil – For each site

Information in red are just guides how to fill out the form, which shall be deleted for submission.

Information shall be grouped per participants.

There is no determination of submission frequency for Adverse Events Table, and it is the investigator´s site SOP discretion/ SOP site or as determined by CEP.

SAE opening date	Participant Code	SAE Code	SAE Classification	Occurrence discrimination	Type of SAE	Causality with the investigational product and the research procedure	Assistance provided to the participant	Date of last updating	Participant´s status at the last updating date	Description of participant´s discontinuity from research
SAE identification date	Participant code in the study	SAE code according to the sponsor clinics sheet (for instance: AE0001)	Classify as Index our Subsequent. In case of index / subsequent relation among events is not clear in investigator´s assessment, event can be classified as index	Verbatim/ Event/ Diagnosis	Seriousness Criterion Severity Criteria: Death, Threat or risk of life, Need of hospitalization, Extension of pre--existent hospitalization; Disability or permanent damage; Congenital anomaly; or Significant medical occurrence	According to the reported in the sponsor clinical form	Describe corrective treatment carried out to the SAE	Event follow-up last date	Inform “in progress”, “recovered without sequels”, “recovered with sequels” and “death” according to the participant general status	Inform whether the participant goes on with the investigation product use and with protocol visits. In negative case, justify

4.2 – Consolidated report for events occurred in Brazil

This template can be used both for Consolidated report of each site and to the Consolidated Report containing information from all Sites related to SAEs occurred in Brazil;

It shall be included in the **trial Partial** and **Final** Reports;

Data to be submitted will refer to the report period (non-cumulative).

SAEs absolute distribution[1]	Quantity of SAEs occurred in the report period
Quantity of participants in the research	TOTAL quantity of participants in the clinical research site

[1]Absolute distribution of SAEs corresponding the total number of serious adverse events occurred in the report period. This number may not be equals to the quantity of participants who had serious adverse events, as one participant can have shown more than one event.

SAEs relative distribution

Types of SAEs[2]	Related		Non-related		Total	
	Absolute value	Relative rate	Absolute value	Relative rate	Absolute value	Relative rate
Death						
Threat or risk of life						
Need of hospitalization / Extension of pre-existent hospitalization						
Disability or permanent damage						
Congenital anomaly						
Significant medical occurrence						
Total[3]						

[2]Typer of SAEs corresponds the seriousness criteria of each SAE, as described in item 3.4 of the Circular Letter No. 13/2020-CONEP/SECNS/MS.

[3]Table values can have differences between SAE absolute quantity and the total absolute value, as the same participant can present a serious adverse event that has more than one seriousness criteria, which will result in a total absolute value greater than the SAE total number.

The field “absolute value” will be filled out with the sum of each seriousness criteria.

The field “relative rate” will be based on **total of participants** quantity in the clinical research site.

For Consolidated Report with the information from **all the sites**, values shall be added.

Notes [1], [2] and [3] will be included in the template report in order to explain possible discrepancies between data.

• **Detailed description of cases in which there is sequel or death due to the participation in the research (and not for disease progression).**

In case any SAE meets the death or disability criteria, or permanent damage, the case narrative shall be provided by the investigator.

Participant Code: Participant code according to the sponsor clinics sheet

Occurrence description: Verbatim/Event/Diagnosis

Detailed description: Description provided by the Investigator

In case there is no event that meets such criteria, inform that there were no events meeting the criteria above.

• **Detailed description of the cases that require compensation of other type of judicial demand.**

In case SAE requires compensation or other type of judicial demand, case narrative shall be performed by the Investigator.

Participant Code: Participant code according to the sponsor clinics sheet

Occurrence description: Verbatim/Event/Diagnosis

Detailed description: Description performed by the Investigator

In case there is no event that meets such criteria, inform that there were no events that required compensation or other type of judicial demand.

4.3 – Consolidated report for international adverse events

This template will be used only to Consolidated Reports **containing International** SAEs;

It shall be included in **trial Partial and Final** Reports;

Data to be submitted will refer to the report period (non-cumulative).

SAEs absolute distribution[1]	Quantity of SUSAR occurred in the report period
Quantity of participants in the research	TOTAL quantity of participants in the research internationally (do not include the quantity of participants in Brazil)

[1]Absolute distribution of SAEs corresponding the total number of serious adverse events, related and unexpected, occurred in the report period. This number cannot be equals to the quantity of participants who had serious adverse events, related and unexpected as one participant can have shown more than one event.

4.3.1 – SAEs relative distribution

Types of SAEs[2]	Total of serious events, related and unexpected[4]	
	Absolute Value	Relative Value
Death		
Threat or risk of life		
Need of hospitalization / Extension of pre-existent hospitalization		
Disability or permanent damage		
Congenital anomaly		
Significant medical occurrence		
Total[3]		

[2]Type of SAEs corresponds to the severity criteria of each SAE, as described in item 3.4 of the Circular Letter No. 13/2020-CONEP/SECNS/MS.

[3]Table values can have differences between SAE absolute quantity and the total absolute value, as the same participant can have present a serious adverse event that has more than one seriousness criteria, which will result in a total absolute value greater than the SAE total number.

[4]For Consolidated Report of international SAEs, only events that meet SUSAR (Suspected Unexpected Serious Adverse Reaction) criteria, i.e., serious events, related and unexpected

The field "absolute value" will be filled out with the sum of each seriousness criteria, even if an event fall under more than one seriousness criteria.

The field "relative value will be based on **total of participants** in the protocol.

Notes [1], [2], [3] and 4 will be included in the template report in order to explain possible discrepancies between data.

• **Detailed description of cases in which there is sequel or death due to the participation in the research (and not for disease progression)**

In case any SAE meets the death or disability criteria, or permanent damage, narrative can be translated

Participant Code: SAE code according to the sponsor clinics form

Occurrence description: Verbatim/Event/Diagnosis

Detailed description: Narrative translation

In case there is no event that meets such criteria, inform that there were no events meeting the criteria above

5 – CONCLUSION

Considering clarifications mentioned and adequacy proposals referring to the Circular Letter No. 13/2020-CONEP/SECNS/MS described herein, the proposal is for harmonization for companies' practice, also to present templates that will serve as guide for notification submissions via CEP/CONEP System.

EXPEDIENT

Publication and content prepared by the Clinical Research and Pharmacovigilance Working Groups of the SINDUSFARMA (Pharmaceutical Industry Union) and ABRACRO (Brazilian Association of Representative Organizations of Clinical Research) /Authorized reproduction provided the source is cited.