HEALTH SECTOR
NATIONAL INSTITUTE OF HEALTH

THE REPUBLIC OF PERU
[COATS OF ARMS]

No.***160-2019-OGITT/INS***

DIRECTOR'S DECISION

Lima, March 22nd, 2019

Upon examination of File **No. 10750-2018** and Report No. *321*-2019-OEI-OGITT-OPE/INS, by the Executive Research Office of the National Institute of Health's General Office of Research and Technology Transfer, by which the approval of the research protocol is requested;

WHEREAS:

Sub-paragraph XV of the Preliminary Title of Law No. 26842, General Health Law, establishes that the State promotes scientific and technological research in the field of health;

Item a), sub-paragraph 136.1, article 136 of Supreme Decree No. 008-2017-SA, which approves the Regulations of the Ministry of Health's Organization and Functions, which states that the National Institute of Health is a Public Body attached to the Ministry of Health; in accordance with Legislative Decree No. 1161, Law on the Organization and Functions of the Ministry of Health, which sets forth in Articles 3 and 4 that the Ministry of Health is the Governing Body of the Health Sector and covers among several matters within the scope of its competence, Health Research and Technology;

As provided for in Article 5 of the Regulations on the Organization and Functions of the National Institute of Health, approved by Supreme Decree No. 001-2003-SA, the Institute has the mission to promote, develop, and disseminate scientific and technological research and the rendering of services in fields of public health, control of communicable and non-communicable diseases, food and nutrition, production of biological products, quality control of food, pharmaceuticals and related products, occupational health, and environmental protection with a focus on human health and intercultural health, in order to contribute to improving the population's quality of life.

Article 6 of the above mentioned Regulations determines the institutional strategic objectives of the National Institute of Health, among others, the development of research in health for risk prevention, protection from harm, health recovery, and rehabilitation of people's capabilities;

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It is necessary to adequately comply with articles 20° "Clinical trials on women and men with reproductive potential," 108° "Responsibilities of the sponsor," 109° "Responsibilities of the principal investigator," and 110° "Reporting of adverse events and adverse reactions" of the Regulations on Clinical Trials approved by Supreme Decree No. 21-2017-SA, in order to provide users with adequate information based on technical knowledge and supported by current applicable international and national standards.

For the purpose of guiding sponsors, contract research organizations, and investigators in the preparation of adverse event reports, the External User Guide for Clinical Trial Safety Reporting is prepared in order to ensure that the information provided is of high quality, with reliable and timely data that contribute to making decisions to protect the well-being of research subjects in the safety report.

With the endorsement of the Executive Director of the Research Executive Office of the National Institute of Health's OGITT;

IT IS HEREBY DECIDED:

Article 1.- To APPROVE the document called **"External User Guide for Clinical Trial Safety Reporting"**, specified in the attached annex, which is an integral part of this Decision for the reasons described in the recitals of this Decision.

Article 2.- To DETERMINE that the General IT Office - OGIS, proceeds (within the framework of its competencies) with the corresponding publication of this Decision in the institutional web portal of the National Institute of Health.

To be registered and notified,

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NORA ESPIRITU SALAZAR, MD
Director General
General Office of Research and Technology Transfer
NATIONAL INSTITUTE OF HEALTH

EXTERNAL USER GUIDE FOR CLINICAL TRIAL SAFETY REPORTING

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Director's Decision No. *160*-2019-OGITT-INS DATE: *March 22nd, 2019*

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EXTERNAL USER GUIDE FOR CLINICAL TRIAL SAFETY REPORTING

I. Introduction

The guide is developed to help sponsors, contract research organizations, and investigators to meet safety reporting requirements that are to be submitted throughout the development of the investigational product and the execution of the clinical trial.

Therefore, it is incumbent upon the General Office of Research and Technology Transfer (OGITT) of the National Institute of Health to establish an external user guide for clinical trial safety reporting.

II. Purpose

To ensure that the information provided by the sponsors or their representatives is of high quality, with reliable and timely data that contribute to making decisions to protect the well-being of research subjects.

III. Objective

To guide the inspected subjects for the adequate notification of safety reports and the actions to be taken based on the safety information coming up in the conduct or execution of clinical trials in Peru in compliance with the obligations set forth in the Regulations on Clinical Trials approved by Supreme Decree No. 021-2017-SA.

IV. Scope of Application

This Guide is applicable to the Sponsors and the Institutions that legally represent them in the country, with respect to their obligations to notify the General Office of Research and Technology Transfer (OGITT) of the safety reports indicated in the Regulations on Clinical Trials and that are related to: serious adverse events, serious adverse reactions, suspected unexpected serious adverse reactions, reporting of pregnancies in the conduct of clinical trials, annual safety reports of investigational products, and any findings that could adversely affect the safety of research subjects or have an impact on the conduct of the study or disrupt the benefit/risk balance.

V. Operational Definitions

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- **Clinical Trials Regulatory Authority:** The National Institute of Health (INS, according to its Spanish acronym) is the authority responsible at the national level for ensuring compliance with the Regulations on Clinical Trials and related rules governing the authorization and conduct of clinical trials, as well as issuing any additional provisions required for their implementation.

- **Benefit/Risk:** The balance between the benefit of the clinical trial resulting from treatment with the investigational product and adverse events.

- **Causality:** Outcome of the imputability analysis and initial assessment of the relationship between the administration of a pharmaceutical product and an adverse reaction. It leads to the determination of a category of causality: definitive, probable, possible, conditional, or unlikely. It allows determining a category of causality.

- **Council for International Organizations of Medical Sciences (CIOMS) Report or Form:** Notification of suspected unexpected serious adverse reactions occurring internationally, which are provided to the National Institute of Health's OGITT. The CIOMS format must be used.

- **Development International Birth Day (DIBD):** This date is the first authorization or approval to conduct a clinical trial in any country.

- **Adverse Event:** Any event or situation detrimental to the health of the research subject, to whom an investigational product is being administered, and which does not necessarily have a causal relationship with the administration of the product. Therefore, an adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational product, whether or not it is related to the investigational product.

- **Serious adverse event:** Any adverse event that results in death, is life threatening for the research subject, requires or prolongs inpatient hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or malformation. For reporting purposes, events may also be considered serious when, based on medical judgment, they may jeopardize the research subject or require intervention to prevent one of the outcomes listed above in this definition.

- **Investigator:** A professional in charge of conducting a clinical trial at a research site because of his or her scientific background and professional experience.

- **Principal investigator:** An investigator in charge of the team of investigators who conduct a clinical trial at a clinical trial site.

- **Contract Research Organization (CRO):** A public or private, national or foreign organization to which the sponsor transfers some of its tasks and obligations by signing a contract.

- **MedDRA:** Medical Dictionary for Regulatory Activities - medical terminology used to classify adverse event information associated with the use of pharmaceuticals and other medical products (e.g., medical devices, biologics, biosimilars, and vaccines). Coding data to MedDRA terminology allows drug regulatory authorities and the pharmaceutical industry to exchange and analyze data related to the safe use of pharmaceuticals more rapidly.

- **Urgent safety measures:** Measures that must be taken to eliminate an immediate hazard for the health or safety of the research subject.

- **Investigational product:** A pharmaceutical product or medical device that is investigated or used as a comparator in a clinical trial, including products with a marketing authorization when used or combined, in formulation or packaging, in a manner different from that authorized, or when used to treat an unauthorized indication, or to obtain more information about its authorized use. For the purposes of this guide, the terms "pharmaceutical product" and "medical device" refer to the provisions of Law No. 29459, Law of Pharmaceutical Products, Medical Devices, and Healthcare Products.

- **Risk:** Probability of developing an unintended outcome related to the quality, safety, or efficacy of the investigational product with respect to the research subject.

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- **Important identified risk and important potential risk:** Identified risk or potential risk refers to those risks that could have an impact on the benefit/risk balance of the investigational product or on the implications for the public health system.

- **Expedited report:** Safety outcome meeting the criteria for serious adverse event or serious adverse reaction, unexpected adverse reaction, and suspected treatment-related events.

- **Adverse reaction:** Any adverse event in which there is a clearly defined causal relationship with an investigational product or there is at least a reasonable possibility of a causal relationship, which occurs regardless of the dose administered.

- **Serious adverse reaction:** Any adverse reaction that results in death, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or malformation. For reporting purposes, events may also be considered serious when, based on medical judgment, they may jeopardize the research subject or require intervention to prevent one of the outcomes listed above in this definition.

- **Unexpected adverse reaction:** An adverse reaction whose nature or severity is not consistent with the investigational product, i.e., it is not described in the investigator's brochure and/or technical data sheet.

- **Reas-Net:** Serious Adverse Events Virtual Reporting System.

- **Suspected Unexpected Serious Adverse Reaction (SUSARs):** Any serious adverse event in which there is at least a reasonable possibility of a causal relationship with the investigational product and whose nature or severity is not described in the investigator's brochure and/or technical data sheet.

VI. General Aspects

6.1. Reporting of adverse events and serious adverse reactions in clinical trials approved in our country

a) The principal investigator provides information to the sponsor no later than one (01) calendar day after becoming aware of serious adverse events, serious adverse reactions, and suspected unexpected serious adverse reactions.

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b) The sponsor evaluates, categorizes, and reports all serious adverse events, serious adverse reactions, and SUSARs occurring in our country. Notification is given within a maximum of 7 calendar days after the event or after becoming aware of the event.

c) Reporting is done through Reas-Net, completing the online form FOR-OGITT-046 “Serious Adverse Event Report” that must be submitted at the reception desk of the OGITT.

d) The notification of the initial report is completed with the necessary information, within the following 8 calendar days. Otherwise, follow-up reports shall be sent and when the follow-up is completed, the final report shall be sent.

e) If the investigator's causality assessment of the serious adverse event differs from the sponsor's causality assessment, the sponsor may not modify the investigator's causality assessment.

6.2. Drafting and quality of the serious adverse event report

a) For the description and diagnosis of the serious adverse event, serious adverse reaction or suspected unexpected serious adverse reaction, the MedDRA or WHO dictionary shall be used.

b) The objective of writing the report is to describe the relevant and related clinical information as a comprehensive and stand-alone "medical story." The information should be presented in a logical time sequence (ideally this should be presented in the chronology of the patient's experience, rather than in the chronology in which the information was received), describing the patient's characteristics, treatment details, medical history, clinical course of the event(s), the diagnosis and serious adverse events including outcome, laboratory tests (including normal ranges), and information supporting or disproving a serious adverse event. In follow-up reports, new information should be clearly identified.

c) Abbreviations and acronyms should be avoided, with the exception of laboratory parameters and units. Key information from supplementary records should be included in the report.

d) The Legal Representative in the country shall submit these reports: initial, follow-up, final, and initial/final, according to specific fields. If two initial reports have been generated for the same patient, the system will send a message indicating that the initial report has already been submitted.

e) No changes can be made to information related to the patient code, research site, and serious adverse event of the form FOR-OGITT-046 "Serious Adverse Event Report."

f) In case the notifier identifies that the serious adverse event report *contains other types of incorrect information* (which are not the fields described in section e) and were submitted through Reas-Net, he or she must justify the reasons for the change by means of a document that must be submitted at the reception desk of the OGITT.

g) In exceptional situations where the notifier requests the *nullity of the report*, he or she must justify the reasons for such action and submit a document at the reception desk of the OGITT. Subsequently, the corresponding changes will be made.

h) Considerations to be taken into account for the nullity of the report:

- In the case of nullity of an Initial Report, if it has follow-up reports (1), (2), (n) and it is only required to eliminate the *Initial Report*, the OGITT will proceed to eliminate all the reports submitted including the follow-up reports, due to the fact that when the initial report is eliminated, the content of the report is lost. Therefore, the Legal Representative in the country will have to re-submit the *information of the initial report and follow-ups*. REAS_NET will assign a new Serious Adverse Event number, as well as a new reporting date to the OGITT-INS.
- If a final report is required to be eliminated, the corresponding permits will be granted. Later, this final report will become a follow-up report and may continue with other follow-up reports up to the conclusion generated by the final report.

6.3. Non-serious adverse events

a) The sponsor will report non-serious adverse events in the progress reports of the clinical trial FOR-OGITT 054 "Clinical Trial Progress Report."

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6.4. Reporting of safety findings

a) If the sponsor is aware of safety findings that do not fall within the definition of a serious adverse event or suspected unexpected serious adverse reaction (SUSAR), these safety findings

require another measure or action such as: an urgent safety measure, protocol or informed consent amendment, suspension or termination of the clinical trial.

b) This information must be notified to the OGITT through a detailed report that includes the measures and actions taken at the local and international levels, if these have already been established. It must also be notified to the Institutional Research Ethics Committees (CIEI, according to its Spanish acronym) and to the investigator within 7 calendar days after the sponsor became aware of it.

c) The information of safety findings must be submitted in Spanish and English. It must be electronic (contained in a CD) and submitted at the document processing department of the National Institute of Health's OGITT.

d) Without prejudice to the deadlines for the reporting of safety findings, the sponsor will subsequently initiate the applicable administrative procedures regarding the measure or action taken and in accordance with the requirements established by the regulations on clinical trials. Some examples are shown below:

Examples of findings (*) to be reported (Art.108, sub-paragraph h)	Immediate measure	Procedures that were initiated after reporting to the OGITT
Lack of efficacy observed in one of the development program protocols (did not meet the primary endpoint for efficacy)	- The administration of the product is interrupted in all Clinical Trials where it is administered. - The study visits and assessment of the participants will continue in accordance with the protocol.	Termination of the Clinical Trial
New safety information related to 257 cases of severe skin reactions, including Stevens Johnson syndrome / Toxic Epidermal Necrolysis, which have been found to be associated to the Investigational Product, post-marketing; information reported by a foreign drug Regulatory Agency.	- Immediate interruption of the Investigational Product in the cases of serious skin reaction (Stevens Johnson syndrome or Toxic Epidermal Necrolysis). - Information to the research subjects, as soon as possible, either directly or by telephone, with regard to possible cases of serious skin reactions, with an emphasis on immediate communication with their corresponding research site. - Notification to the Ethics Committees and regulatory agencies.	- Update the Investigator's Brochure - Informed Consent Form Amendment
Interim results from Week 24 of Study X in HIV patients show increased gastrointestinal intolerance and emerging resistance to treatment with the investigational product compared to the comparator arm.	- Discontinue the study treatment. - Transition to an alternative antiretroviral therapy against HIV. - Follow-up visits to research subjects.	Termination of the Clinical Trial
A possible sign of "increased risk of hemorrhagic complications" was observed in a routine review of safety data in several Clinical Trials of an investigational product development program.	- Interruption of screening and recruitment activities in all Clinical Trials that evaluate the investigational product either as monotherapy or in combination. - Inform all participants of the possible risk of bleeding identified.	Amendments to the protocol. Amendments to the consent form.

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* One that could adversely affect the safety of the research subjects, have an impact on the conduct of the study, or disrupt the benefit/risk balance.

6.5. Notification of international CIOMS reports

a) The sponsor quarterly or semi-annually notifies CIOMS reports of suspected unexpected serious adverse reactions occurring internationally on magnetic media (CD).

b) The sponsor only submits the hard copies that are requested in Annex 1.

6.6. Annual Development Safety Update Report (DSUR)

a) The DSUR is prepared after the first authorization of the clinical trial in any country. The DIBD will be taken into account as the time of reference.

b) The DSUR development structure follows the ICH *"Guidance for Industry E2F Development Safety Update Report."*

c) The Sponsor must complete online the form FOR-OGITT-048 "Summary of the annual safety report of the investigational product" in Spanish according to the fields or data requested; the inspected subject must not reference the data requested from the form FOR-OGITT-048 to the DSUR document.

d) The Sponsor submits at the OGITT's reception desk: form FOR-OGITT-048 "Summary of the annual safety report of the investigational product" and the DSUR on magnetic media (CD).

6.7. Reporting of pregnancy

a) When the sponsor becomes aware of pregnancy cases through the investigator, notification will be made by means of Reas-Net, completing online form FOR-OGITT-047 "Notification of pregnant women and newborns in clinical trials" to be submitted at the reception desk of the OGITT.

b) The sponsor submits form FOR-OGITT-047 "Notification of pregnant women and newborns in clinical trials" on magnetic media (CD), as well as the procedures for the monitoring and control of the pregnancy and the newborn.

c) Pregnancy reporting time may not be longer than 7 calendar days.

6.8. Reporting of Post-Study adverse events

a) The sponsor or their representative to whom safety reporting functions have been delegated, must send an email to consultaensayos@ins.gob.pe to coordinate with the IT manager and have access granted to the Reas-Net System.

b) When access is granted through Reas-Net, form FOR-OGITT-046 "Serious Adverse Event Report" must be completed and submitted to the OGITT's reception desk.

c) Serious Adverse Reaction Reports or Serious Adverse Event Reports occurring after the completion of the clinical trial should be kept in the research site's file.

VII. Responsibilities

7.1. Sponsor's responsibilities with regards to the safety report

a) The sponsor must ensure that the investigator's brochure specifies and lists the adverse events observed with the investigational product and those for which there is a confirmed or suspected causal relationship. In addition, the investigator's brochure should list the adverse events that commonly occur with other classes of drugs or those that they can predict that will occur based on the pharmacological properties of the investigational product, even if not observed with the investigational product in order to alert the principal investigator of the

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possibility of their occurrence. The sponsor, based on their own information or other information, shall determine which terms accurately reflect an adverse event, including the names of the syndrome, if applicable.

b) The sponsor must describe in the protocol the serious adverse events that will not be reported expeditiously because they are anticipated to occur in the study population with a certain frequency regardless of the exposure to the investigational product.

c) The sponsor must describe in the protocol the procedures for monitoring serious adverse events that are produced by the investigational product.

d) Depending on the clinical trial design, the pathology, and the investigational product, the sponsor shall describe in the protocol the procedures for the reporting of non-serious adverse events.

7.2 Principal investigator's responsibility for the safety report

a) The principal investigator should report serious adverse events, serious adverse reactions, and suspected unexpected serious adverse reactions occurring in our country to the sponsor Contract Research Organization, and Institutional Research Ethics Committee when the event takes place or becomes known within 1 calendar day.

b) The principal investigator must record *non-serious adverse events* and report them to the sponsor in accordance with the procedure described in the study protocol.

c) When the principal investigator becomes aware of *serious adverse events or serious adverse reactions* that occur after the completion of the clinical trial, he or she must notify the sponsor or Contract Research Organization and the Institutional Research Ethics Committee.

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ANNEX 1: CIOMS INTERNATIONAL

NCT Clinical Trials.Gov/ EUDRA CT number	Research subject number or ID	Age	Gender	Country	Investigational Product	Dose and route of administration	Serious Adverse Event MedDra	Start date	End date	Severity criterion Outcome	Length of treatment	Causality
NCT03485859	253042	24	M	USA	XYZ 360	2.9mg/bid orally	hypothyroidism	11-06-18	-------	Serious Hospitalization	352 days	Possible

Notes:

- **ClinicalTrials.gov:** is a database of clinical trials registered in the United States of America.
- **EUDRA CT:** is a database of clinical trials registered in the European Union.
- **Causality:** definitive, probable, possible, conditional, or unlikely.
- **Gender:** M (male) and F (female).

Bibliography

- International Conference on Harmonisation. Guideline Clinical Safety Data Management: Definitions and Standard for Expedited Reporting E2A. [On- line guide] 1994 [Accessed on September 12, 2017.] Available at: http://www.ich.org/fileadmin/PublicWebSite/ICHProducts/Guidelines/Efficacy/E2A/Step4/E2AGuideline.pdf
- European Medicines Agency. Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation Data. [On- line guide] 2004 [Accessed on September 14, 2017). Available at: http://www.ema.europa.eu/docs/enGB/document library/Regulatoryandprocedural guideline/2009/11/WC500011303.pdf
- Food and Drug Administration. Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies. [On- line guide] 2012 [Accessed on September 15, 2017]. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071639.pdf

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