HEALTH SECTOR

NATIONAL INSTITUTE OF HEALTH

No. 043-2024-DIIS/INS

DIRECTOR'S RESOLUTION

Lima, January 30, 2024

Having seen file **No. 00002460-2024,** which contains **Report No. 001-2024-ETIPS-SUDEC-DIIS/INS,** issued by the Sanctioning Procedures Instruction Working Group; and **Note Information No. 139-2024-SUDEC-DIIS/INS,** issued by the Clinical Trials Subdirectorate of the Directorate of Health Research and Innovation, and;

WHEREAS:

That, numeral XV of the Preliminary Title of Law No. 26842, General Health Law, establishes that the The State promotes scientific and technological research in the field of health; furthermore, in its Article 28, it stipulates that experimental research involving humans must adhere to the specific legislation on the subject and to the ethical principles contained in the Declaration of Helsinki and subsequent declarations that update these principles;

That, Article 4-A of Legislative Decree No. 1161, Law on the Organization and Functions of the Ministry of Health, amended by Legislative Decree No. 1504, Legislative Decree that strengthens the National Institute of Health for the prevention and control of diseases, states that the governing authority of the Ministry of Health includes the power to regulate, supervise, inspect, and, where appropriate, sanction, in the areas that comprise health matters. The leadership in health matters within the sector is exercised by the Ministry of Health on its own behalf or, by express delegation, through its attached public agencies, and within the framework and limits established in the aforementioned law, the Organic Law of the Executive Branch, the substantive norms that regulate sectoral activity, and the norms that govern the decentralization process;

That, through literal a) numeral 136.1 of article 136 of the Regulation of Organization and Functions of the Ministry of Health, approved by Supreme Decree No. 008-2017-SA, it is established that the National Institute of Health is a Public Body attached to the Ministry of Health, in accordance with the provisions of Legislative Decree No. 1161, Law of Organization and Functions of the Ministry of Health, which establishes in its articles 3 and 4 that the Ministry of Health is the Governing Body of the Health Sector and includes, among several matters within its scope of competence, those of health research and technology;

That, in this line, articles 1 and 2 of the First Section of the Regulation of Organization and Functions of the National Institute of Health, approved by Supreme Decree No. 016-2023-SA, ratify and specify that the National Institute of Health is a Specialized Technical Public Organization attached to the Ministry of Health;

That, likewise, the Integrated Text of the Regulation of Organization and Functions of the National Institute of Health, approved by Executive Presidential Resolution No. 006-2023-PE/INS, restructures the organization of the National Institute of Health, and should be understood for the purposes of clinical trials,

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that the Head of the National Institute of Health is now called the Executive Presidency of the National Institute of Health; the Directorate of Health Research and Innovation (DIIS) is what was previously known as the General Office of Research and Technology Transfer (OGITT); and the Clinical Trials Subdirectorate replaces the Executive Office of Research (OEI).

That, likewise, numeral 4.2 of article 4 of the Integrated Text of the Regulations of Organization and Functions of the National Institute of Health, the Institute's general functions are the promotion and development of research, technology transfer and innovation in health within the framework of what is established in the National Health Policy and the National Policy of Science, Technology and Innovation, as well as the generation and dissemination of evidence and scientific information in health that contribute to public health actions and interventions; among others;

That, in this sense, article 79 of the Integrated Text of the aforementioned Regulation determines that the Directorate of Research and Innovation in Health - DIIS (formerly, OGITT), is the line, technical, regulatory and service provision body, responsible, among other things, for regulating and standardizing the clinical trials carried out in the country, to contribute to the health of the population;

That, for its part, the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA, in its article 133 establishes that sanctions are imposed by the DIIS (formerly, OGITT) through Directorial Resolution, for which it applies the criteria indicated in article 135 of the General Law of Health, which are as follows: i) the damage that has occurred or may occur to people's health; ii) the seriousness of the offense; and iii) the offender's repeat or repeat offense status;

That, article 132 of the aforementioned Regulation establishes that those who commit infractions classified in its article 131, will be liable to one of the following administrative sanctions: a) Warning, b) Fine between half (0.5) and one hundred (100) Tax Units, c) Closure of a research center for a clinical trial, d) Cancellation of the research center registration, e) Cancellation of the clinical trial, f) Restrict the researcher from carrying out future trials for a period to be determined by the OGITT of the INS according to the level of severity of the infraction;

That, Article 247 of the Single Ordered Text of Law No. 27444, Law of Administrative Procedure General, approved by Supreme Decree No. 004-2019-JUS, establishes that the special rules of administrative sanctioning procedure must necessarily apply the principles of the administrative sanctioning power referred to in article 248 of the same normative body, as well as the structure and guarantees provided for the administrative sanctioning procedure;

That, Article 248 of the TUO of Law No. 27444 enshrines the principle of reasonableness, by virtue of which the commission of sanctionable conduct should not be more advantageous for the offender than complying with the infringed rules or assuming the sanction. However, the sanctions to be applied must be

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proportional to the non-compliance classified as an infraction, observing the grading criteria established therein;

That, numeral 5 of article 255 of the aforementioned rule establishes that the authority in charge of the administrative sanctioning procedure must formulate a final investigation report in which the proposed sanction is determined in a reasoned manner;

That, by Chief Resolution No. 064-2021-J-OPE/INS, dated March 23, 2021, the procedure for the application of sanctions in the regulatory framework of Clinical Trials was approved, establishing in its section 4.2.2) that the infractions in the regulatory framework of clinical trials may be: a) minor infractions, b) serious infractions, c) very serious infractions;

That, by Directorial Resolution No. 336-A-2021-OGITT/INS, dated August 12, 2021, the General Office of Research and Technology Transfer of the National Institute of Health, approved the "Methodological Guide for Graduation of Fines for Non-Compliance with the Clinical Trials Regulations";

That, by Supreme Decree No. 018-2023-SA, the Regulation for the application of sanctions related to violations of the Clinical Trials Regulation, approved by Supreme Decree, was approved. No. 021-2017-SA, which regulates and establishes the scale of sanctions to be imposed as a consequence of the commission of infractions for non-compliance with the provisions established in the Regulations of Clinical Trials;

That, the first final complementary provision of Supreme Decree No. 018-2023-SA, which approves the Regulations for the application of sanctions related to violations of the Testing Regulations Clinical, establishes that the National Institute of Health, through Resolution of the OGITT (now, DIIS), updates the methodology for calculating sanctions to be applied within the framework of the Sanctions Regulation, when it deems it necessary;

That, through Registry No. 24384-2023, the DIIS requested the contracting of specialized consulting services to update the methodology for calculating sanctions in the Methodological Guide for the graduation of fines for non-compliance with the clinical trials regulations, within the framework of the implementation of the first complementary provision of Supreme Decree No. 018-2023-SA;

That, as a result of the aforementioned contract, the document called "Methodological Guide for Graduation of Sanctions for Non-compliance with the Clinical Trials Regulations", which contains the process of graduation of monetary and non-monetary sanctions to be imposed on the inspected agents, in accordance with the provisions of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA;

That, through Report No. 001-2024-ETIPS-SUDEC-DIIS/INS, the Working Group on the Instruction of Sanctioning Procedures of the Sub-directorate of Clinical Trials of the Directorate of

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The National Institute of Health's Research and Innovation in Health recommends the approval of the Methodological Guide, since it will be a tool that will allow for reasonable and proportional application of sanctions to be imposed on violators of the Clinical Trials Regulations, observing the grading criteria contained in the General Health Law and in the TUO of Law No. 27444;

That, through Information Note No. 139-2024-SUDEC-DIIS/INS issued by the Subdirectorate of Tests Clinicians, the aforementioned Report is sent to the Directorate of Health Research and Innovation;

That, according to the information provided by the Procedures Instruction Working Group Sanctioners, it is concluded that it is necessary to update the current Sanctions Guide, in compliance with the provisions of the first final complementary provision of the Regulations Sanctions;

That, in light of the above, the Methodological Guide for Graduation of Sanctions should be approved Failure to comply with the Clinical Trials Regulations, thereby ensuring due process when determining the sanction to be imposed, protecting the rights of those administered;

With the approval of the Deputy Director II (t) of the Subdirectorate of Clinical Trials of the Directorate of Health Research and Innovation of the National Institute of Health;

In accordance with the provisions of Law No. 26842, the General Health Law; the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA; the Regulation on the Application of Sanctions Related to Violations of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA, approved by Supreme Decree No. 018-2023-SA; the Consolidated Text of Law No. 27444, the General Administrative Procedure Law, approved by Supreme Decree No. 004-2019-JUS; and in exercise of the powers established in paragraph m) of article 80 of the Integrated Text of the Organization and Functions Regulations of the National Institute of Health, approved by Executive Presidential Resolution No. 006-2023-PE/INS;

IT IS RESOLVED:

Article 1.- APPROVE the document called **"METHODOLOGICAL GUIDE FOR THE GRADUATION OF SANCTIONS FOR NON-COMPLIANCE WITH THE CLINICAL TRIALS REGULATIONS",** which contains the process of graduating sanctions to be imposed on the inspected agents in accordance with the provisions of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA, and in the Regulations for the application of sanctions related to violations of the Clinical Trials Regulations, approved by Supreme Decree No. 018-2023-SA.

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Article 2.- LEAVE WITHOUT EFFECT the document called **"METHODOLOGICAL GUIDE FOR GRADUATION OF FINES FOR NON-COMPLIANCE WITH THE CLINICAL TRIAL REGULATIONS",** approved by Directorial Resolution No. 336-A-2021-OGITT/INS.

Article 3.- NOTIFY this Resolution to the Office of Information and Communications Technologies - OTIC, so that within the framework of its institutional powers, it proceeds with the corresponding publication on the institutional portal of the National Institute of Health.

Register and communicate,

Dr. LEDA YAMILÉE HURTADO ROCA
Director
Directorate of Health Research and Innovation
National Institute of Health

GRADUATION METHODOLOGICAL GUIDE OF PENALTIES FOR NON-COMPLIANCE OF THE TEST REGULATIONS CLINICIANS

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METHODOLOGICAL GUIDE FOR THE GRADUATION OF PENALTIES FOR NON-COMPLIANCE OF THE CLINICAL TRIALS REGULATION

1. Object

The purpose of this Guide is to provide greater predictability regarding the criteria and components to be considered by the National Institute of Health (hereinafter, INS) for the graduation process of sanctions to be imposed on the inspected agents in accordance with the provisions of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA (hereinafter, the Clinical Trials Regulation); and in the Regulation for the application of sanctions related to violations of the Clinical Trials Regulation, approved by Supreme Decree No. 018-2023-SA (hereinafter, the Sanctions Regulation).

2. Scope of application

This Guide is mandatory for the Clinical Trials Subdirectorate (formerly the Executive Office for Research) in its capacity as investigating authority, the Health Research and Innovation Directorate (DIIS) (formerly the General Office for Research and Technology Transfer) in its capacity as sanctioning authority, and the Executive Presidency (formerly the Headquarters) of the INS in its capacity as reviewing authority, or any organic units that replace them, in the exercise of their respective functions within the framework of the administrative sanctioning procedure for violations of the provisions contained in the Clinical Trials Regulations.

It is also available for consultation by those subject to the INS's sanctioning authority.

3. Definitions

For the purposes of this Guide, the definitions established in section 2.1 of article 2 of the Clinical Trials Regulations apply, to which the following are added:

3.1 Offenders: In accordance with the Sanctions Regulations, the following subjects who fail to comply with the provisions of the clinical trial regulations are considered offenders:

i) the Sponsor;
ii) the Contract Research Organization (CRO);
iii) the Research Institution; or,
iv) the principal investigator.

3.2 Research Institution: These are public or private health establishments duly authorized and categorized by the Ministry of Health or the corresponding health authority, such as hospitals, clinics, specialized health institutes, as well as establishments that comply with the provisions of article 57 of the Regulation.
Clinical Trials, where research centers operate that conduct clinical trials.

3.3 Principal Investigator: Researcher responsible for a team of researchers who They conduct a clinical trial at a clinical trial center.

3.4 Contract Research Organization (CRO): Public or private organization, national or foreign, with legal status recognized in Peru that develops activities in the health field and to which the sponsor transfers some of its tasks and obligations through the signing of a contract.

3.5 Sponsor: An individual, group of individuals, company, institution, or organization with legal representation in the country and duly registered in the corresponding public registries, who assumes responsibility for the initiation, maintenance, completion, and financing of a clinical trial. Sponsor is also considered an independent investigator who initiates and assumes full responsibility for a clinical trial.

3.6 Sanctions: In accordance with the Objective section of this Guide, the INS DIIS may impose, depending on the level of severity of the violation, among others, the following sanctions:

- Warning.
- Fine between half (0.5) and one hundred (100) Tax Units.
- Closure of a research center for a clinical trial.
- Cancellation of the research center registration.
- Cancellation of the clinical trial.
- Restrict the researcher from conducting future trials for a period to be determined by the General Office of Research and Technology Transfer of the National Institute of Health, according to the severity of the violation.

4. Legal Basis

- Law No. 26842, General Health Law.
- Law No. 29459, Law on Pharmaceutical Products and Medical Devices and its regulation.
- Legislative Decree No. 1161, Law on the Organization and Functions of the Ministry of Health.
- Legislative Decree No. 1504, Law that strengthens the National Institute of Health for the prevention and control of diseases.
- Supreme Decree No. 021-2017-SA approving the Clinical Trials Regulations.
- Supreme Decree No. 004-2019-JUS, which approves the Single Ordered Text of the Law No. 27444, General Administrative Procedure Law.
- Supreme Decree No. 016-2023-SA, which approves the First Section of the Regulations of Organization and Functions of the National Institute of Health.
- Supreme Decree No. 018-2023-SA, which approves the Regulation of Sanctions related to violations of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA.

- Supreme Decree No. 014-2020-SA establishes measures to ensure the proper conduct of clinical trials for Covid-19 in the country.

- Ministerial Resolution No. 233-2020-MINSA, which approves the technical document: “Ethical considerations for health research involving human beings.”
- Chief Resolution No. 072-2019-J-OPE/INS, which approves the “Guide for Inspections of Clinical Trials”.
- Chief Resolution No. 096-2020-J-OPE/INS, which approves the creation of the National Transitional Committee on Research Ethics for the evaluation and ethical supervision of clinical trials for Covid-19 disease.
- Chief Resolution No. 097-2020-J.OPE-INS, which approves the management system document called "Authorization Procedure for Conducting Clinical Trials for Covid-19 Disease," within the framework of the national health emergency.

- Headquarters Resolution No. 098-2020-J-OPE-INS, which approves the management system document called “Authorization procedure for carrying out the

Clinical Trials for Covid-19 Disease," within the framework of the national health emergency.

- Chief Resolution No. 139-2020-J-OPE/INS approving "Guidelines for the execution of clinical trials during the Covid-19 health emergency."
- Chief Resolution No. 167-2023-OPE/INS approving the Second Section of the Organization and Functions Regulations of the National Institute of Health.

5. General Provisions

5.1 Institutional Framework

Sections I and XV of the Preliminary Title of the General Health Law, Law No. 26842 (hereinafter, LGS) indicate that health is of public interest and that the State is responsible for its regulation, surveillance and promotion, as well as the promotion of scientific and technological research in health.

For its part, section 9 of Article 3 of Legislative Decree No. 1161, the Law on the Organization and Functions of the Ministry of Health (hereinafter, the LOF), establishes that the Ministry of Health has jurisdiction over health research and technologies. In this regard, section c) of Article 5 of the LOF indicates that one of the guiding functions of said ministry is to supervise and evaluate the implementation of policies, actions, and interventions in health research, innovation, and technologies, epidemiological surveillance, and health intelligence.

Along these lines, Article 28 of the LGS allows experimental research involving human subjects subject to special laws and ethical principles. Under this legal authorization, the Clinical Trials Regulation was issued, which established the procedure for authorization, execution, and post-execution actions following the execution of clinical trials.

Specifically, in line with the above regulations, Article 6 of Legislative Decree No. 1504, the Legislative Decree that strengthens the National Institute of Health for the prevention and control of diseases, establishes that this entity is a specialized technical public body attached to the Ministry of Health with legal status under internal public law, functional, administrative, economic, and financial autonomy, and national jurisdiction in health research, innovation, and technologies, as well as in epidemics, epidemiological surveillance, and health intelligence.

Regarding the scope of the INS's jurisdiction, according to numerals a) and e) of article 6 of Legislative Decree No. 1504, among the areas of public health in which the INS exercises jurisdiction are the prevention and control of communicable and non-communicable diseases, as well as the production of biologicals and goods of strategic importance in public health.

Likewise, among the functions corresponding to the INS, literal i) of article 7 of Legislative Decree No. 1504 indicates that this body supervises the clinical trials carried out in the country. This, with the purpose of protecting the rights, safety, dignity and well-being of the research subjects, determining the

obligations of the persons and entities involved in the approval and execution of clinical trials and to ensure that the data obtained are reliable and robust.

Furthermore, Article 4-A of the LOF, as amended by Legislative Decree 1504, the Legislative Decree that strengthens the National Institute of Health for the prevention and control of diseases, regulates the Ministry of Health's regulatory authority, which includes regulatory, supervisory, oversight, and, where appropriate, sanctioning powers in areas related to health.

The Ministry of Health exercises oversight over health matters within the sector, either on its own initiative or, by express delegation, through its affiliated public agencies, within the framework and limits established in the aforementioned Law, the Organic Law of the Executive Branch, the substantive regulations governing sectoral activity, and the regulations governing the decentralization process.

In this regard, in order to ensure compliance with the regulations on clinical trials, the Clinical Trials Regulation establishes the procedure for authorization, execution and actions following the execution of clinical trials,
granting the INS Research and Innovation Directorate the sanctioning function regarding non-compliance with the obligations contained in these regulations.

5.2 Regulatory Framework:

5.2.1 About violations

According to Article 131 of the Clinical Trials Regulation and the Annex to the Sanctions Regulation, the offending conduct is as follows:

a) Prevent the actions of the inspectors of the regulatory authority duly accredited.

b) Using any investigational product on subjects without the authorization referred to in Article 67 of the Clinical Trials Regulation.

c) Conduct clinical trials without prior authorization from the authority regulatory.

d) Making modifications to the conditions of authorization of the clinical trial or amendments to the research protocol without prior authorization from the regulatory authority. A deviation from the protocol in a research subject required to eliminate an immediate risk or a change approved by the IRB applicable to a research subject that does not constitute an amendment to the protocol does not constitute a violation.

e) Failure to comply with the obligation to report adverse events of the investigational product to the DIIS (formerly OGITT) of the INS.

f) Communicate to the DIIS (formerly OGITT) of the INS any adverse events detected after the deadline established in this Regulation has expired.

g) Failure by the persons and entities participating in the clinical trial to ensure the confidentiality and privacy of the research subject.

h) Carry out the promotion, information or advertising of the product in the research phase.

Y0) Failure to comply with the security measures established by the DIIS (formerly OGITT).

j) Conducting the clinical trial without adhering to the content of the protocols on the basis of which the authorization was granted.

k) Conducting the clinical trial without the informed consent of the research subject or, where appropriate, the person legally authorized to grant it.

l) Failure to comply with the duty to inform the person about the clinical trial in which they are participating as a research subject.

m) Fabricate or falsify the information required by this Regulation or the data related to the trial.

n) Failure to comply with other mandatory provisions established by the Clinical Trials Regulations and the rules emanating from them.

The following infractions arise from the type of infringement contained in literal n):

n.1) Failure to notify the National Authority for Pharmaceutical Products, Medical Devices and Health Products (ANM) and the DIIS of the INS in advance of the destruction of the Research Product. Article 96, literal a) of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-

SA.

n.2) Failure to destroy the unused and/or returned Research Product. Article 96, letter a) of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.3) Failure to notify the INS DIIS of critical, very serious, major, or serious deviations from the authorized conditions of the clinical trial. Article 40, paragraph n) of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017.

SA.

n.4) Failure to notify the INS DIIS of a) publications related to the authorized clinical trial. Article 107 of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.5) Failure to submit to the INS DIIS the progress and final reports of the authorized clinical trial. Literal i) of article 40 of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA. Literal n) of article 52 of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-

SA.

n.6) Failure to request the suspension of the clinical trial when its execution puts the health and safety of the participating subjects at risk. Article 2, paragraph 2.1, subparagraph 45 of the Clinical Trials Regulations, approved by Supreme Decree

No. 021-2017-SA. Article 9 of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.7) Failure to develop culturally appropriate forms and means to communicate the necessary information to Indigenous or Native peoples involved in the trial and thus comply with the informed consent process. Article 25, paragraph c) of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA. Article 9 of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.8) Failure to maintain the insurance policy in force during the execution of the clinical trial. Article 28 of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA. Article

40, literal q) of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA.

n.9) Failure to maintain the financial fund during the execution of the clinical trial. Article 28 of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA. Article 40, paragraph r) of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.10) Failure to notify the OGITT of the change in category of the Research Institution or Research Center. Article 54 of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.11) Failure to maintain the conditions under which the registration of the Research Center was approved. Article 55 of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.12) Failure to comply with the provisions of the Good Clinical Practice Guidelines and Peruvian regulations for conducting clinical trials. Article 52, paragraph b, of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.13) Failure to guarantee the safety of research subjects and decisions affecting their treatment. Article 52, paragraph l) of the Clinical Trials Regulations, approved by Supreme Decree No. 021-2017-SA.

n.14) Failure to report serious adverse events, serious adverse reactions, and suspected and unexpected serious adverse reactions to the sponsor or the OIC and the ICER. Article 109 of the Clinical Trials Regulation, approved by Supreme Decree No. 021-2017-SA.

5.2.2 Objectives of sanctions

Standards regulate the behavior of agents (natural or legal persons) in the face of specific circumstances or events. The mandatory nature of a standard depends on a prior analysis of the desirable outcome for society if it is followed. Thus, ensuring compliance with a standard is associated with ensuring the outcome anticipated at the time of its formulation; therefore, not only must standards be established with a specific objective, but incentives for compliance must also be established.

The construction of these incentives is often associated with the formulation of other rules (sanctioning rules), which seek to sanction non-compliance with the primary rules that regulate agents' behavior. As can be seen, the purpose of sanctioning rules is not to impose sanctions on those governed, but rather to form part of a mechanism that incentivizes compliance with the rule that establishes obligations.

The first approach to ensuring that sanctioning rules form part of a successful compliance mechanism is given by establishing that, for the administered, the benefit of complying with the rule is greater than the benefit of not complying with it (even establishing that the latter could be negative). In this scenario, the application of sanctioning rules must implement an incentive scheme that leads the administered to comply with the rules.

first rules, under the consequence that non-compliance will be penalized, leaving it in a less beneficial situation than compliance.

However, there are situations in which, despite the existence of sanctioning regulations, the administrator decides to violate the initial regulations. Thus, once it has been established that the administrator violated the initial regulations, a sanctioning scheme is then proposed to discourage future noncompliance.

Taking into account this regulatory framework on the powers of the authority and regulations in matters of clinical trials, article 128 of the
LGS points out the following:

> *"Article 128.- In the exercise of the powers conferred upon it by this law, organic laws, laws of organization and functions, other special laws and its regulations, the Health Authority is empowered to arrange for guidance and education actions, conduct inspections of any movable or immovable property, take samples and carry out the corresponding tests, gather information and carry out any other actions it deems pertinent for the fulfillment of its functions, as well as, where applicable, apply security measures and sanctions."*

However, within the specific regulatory framework established for clinical trials, Article 119 of the Clinical Trials Regulation states that the supervision of clinical trials is carried out *to ensure the quality and integrity of the data or other elements, as well as to protect the rights and well-being of research subjects.*

In this sense, the imposition of sanctions has three main objectives:

a) discourage the commission of violations of clinical trial regulations, b) provide equitable and
reasonable treatment to those administered, and c) guarantee the resolution
of procedures for violations of clinical trial regulations.

Regarding the first objective of discouraging violations, the sanction is a mechanism to deter the offender from repeating the sanctioned conduct and, in turn, generally deters other administrators from engaging in the potential violation.

To this end, in line with the principle of reasonableness of the Constitution of Law No. 27444, the sanction must place offenders in a more disadvantageous position than they would have been in had they not committed the violation; this means that the offender should not receive or should have any illicit benefits obtained as a result of noncompliance with the regulations removed.

In other words, the primary objective of administrative sanctions is to deter or discourage the commission of violations by those governed. This implies that the magnitude of these sanctions must be equal to or greater than the expected benefit of committing the violations. The objective is to ensure that administrative sanctions truly have a deterrent effect, not only on the offending agent but also on all other agents. Nevertheless, the authority has the option of graduating the sanction.

increasing or reducing it, depending on the respective aggravating or mitigating criteria that are applicable in each specific case.

The second objective is to provide reasonable and proportional treatment to those affected. This allows citizens to become aware of the need to comply with the law by associating the sanction with a concept of "fairness." A disproportionate sanction may actually act as a disincentive to comply with the law and engage in economic activities.

The third objective is to ensure the resolution of proceedings for violations of clinical trial regulations. Considering the importance of scientific research and clinical trial procedures to society, the State's actions should facilitate the resolution of proceedings and save resources that could be allocated to other purposes, such as monitoring new violations.

5.2.3 Types of sanctions

According to the Constitutional Court, Administrative Sanctioning Law and Criminal Law derive from the same *ius* puniendi *of the State;* however, the truth is that criminal sanctions and administrative sanctions cannot be equated, given that the former have a re-educational and social reintegration purpose, while the latter have a purely repressive purpose.1

Along these lines, the sanctions contemplated in the Sanctions Regulations may be monetary or non-monetary. The same Regulations establish that the DIIS may impose the following sanctions on the Sponsor, the Contract Research Organization, the research institution, or the principal investigator:

a) **Warning:** A non-monetary sanction applicable to offenses considered minor and intended to prevent the offender from repeating the same offense. According to legal doctrine, a warning "...consists of a warning or a warning about the offense committed." 2

b) **Fine between half (0.5) and one hundred (100) Tax Units:** The fine is the most common and characteristic monetary sanction, which imposes on the offender an obligation to give a sum of money to the Administration. In the present case, since it is subject to minimum and maximum margins, the principle of reasonableness applies to the calculation of the final fine, whereby the authority must foresee that the commission of the sanctionable conduct is not more advantageous for the offender than complying with the infringed rules or assuming the sanction. Likewise, the principle of non-confiscation applies, whereby the amount of the fine cannot significantly affect the assets of a person that puts their financial viability at risk.

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1 Judgment of September 3, 2010, issued by the Constitutional Court, in the amparo process, processed under File No. 01873-2009-PA/TC.

2 JORDANO, Jesús. *"The Sanctioning Power of the Administration."* In: Lectures on Administrative Law – General Section. Concepción Barrero (Coordinator). Tecnos Publishing House. Third Edition. Madrid. Page 83.

c) **Closure of a research center for a clinical trial:** Non-monetary sanction consisting of the temporary suspension of the qualifying title held by the offender, for the exercise of a particular research activity.

d) **Cancellation of the research center registration:** Non-monetary sanction consisting of the permanent deprivation or revocation of the enabling title held by the offender, for the exercise of any research activity.

e) **Cancellation of the clinical trial:** Non-monetary sanction consisting of the definitive interruption of the permission granted to the sponsors or Contract Research Organization to carry out a particular research activity.

F) **Restrict the researcher from conducting future trials for a period to be determined by the Directorate of Health Research and Innovation** of the National Institute of Health, in accordance with the
Level of severity of the violation: Non-monetary sanction consisting of the temporary suspension of the permit, license or other enabling title that authorizes the researcher to conduct clinical trials.

In this regard, depending on the severity, the authority may impose sanctions as follows:

ÿ **To Sponsors and/or Contract Research Organizations:**

a) Minor infractions: Warning or fine of up to twenty (20) Tax Units (UIT).

b) Serious violations: Fine from twenty-one (21) Tax Units (UIT) to sixty (60) Tax Units (UIT) or cancellation of the clinical trial.

c) Very serious violations: Fine from sixty-one (61) Tax Units (UIT) to one hundred (100) Tax Units (UIT) or cancellation of the clinical trial.

ÿ **To the Research Institution:**

a) Minor infractions: Warning or fine of up to twenty (20) Tax Units (UIT).

b) Serious violations: Fine from twenty-one (21) Tax Units (UIT) to sixty (60) Tax Units (UIT) or closure of a research center for a clinical trial.

c) Very serious infractions: Fine from sixty-one (61) Tax Units to one hundred (100) Tax Units (UIT), or cancellation of the research center registration.

ÿ **To the Principal Investigator:**

(The restriction period for conducting future trials for the researcher is a minimum of one (01) month up to a maximum of five (05) years.)

a) Minor infractions: Warning or fine of up to twenty (20) Tax Units (UIT).

b) Serious violations: Fine from twenty-one (21) Tax Units (UIT) to sixty (60) Tax Units (UIT), or restriction on the researcher from carrying out future trials for a period of up to three (03) years.

c) Very serious violations: Fine from sixty-one (61) Tax Units (UIT) to one hundred (100) Tax Units (UIT), or restriction on the researcher from carrying out future trials for a period of up to five (05) years.

In this regard, for the purposes of this Guide, this methodology will include the graduation of two types of sanctions:

i) A fine between half (0.5) and one hundred (100) UIT; and
ii) Non-monetary sanctions.

5.2.4 Principles of the graduation of sanctions

The principles applicable to determining sanctions are as follows:

- **Reasonableness:** The sanction must maintain a due proportion between the means and the ends to be protected, so that they respond to what is strictly necessary to achieve their objectives.

  Thus, the sanction must be adequate to deter the conduct; the authority must assess whether alternative means exist and weigh the intensity of the conflicting principles.

- **Predictability:** Sanctions must be based on objective information and, unless duly motivated, be consistent with established practice and methodology.

- **Deterrence:** Sanctions should prevent the offending agent from benefiting from breaking the law.

- **Social Efficiency:** In addition to the need to impose a sanction, in order for society's situation to be better than if it were not imposed, the total cost of imposing the sanction (estimation, application, and collection) must be minimal and lower than that of the sanction.

5.2.5 Criteria for grading sanctions

According to Article 135 of the General Health Law, the graduation of the sanction must consider the following criteria:

a) the damage caused or potential damage to people's health, b) the seriousness of the violation and
c) the condition of recidivism.

For its part, section 3.4 of article 3 of the Sanctions Regulation stipulates that monetary or non-monetary sanctions are applied considering as an aggravating factor the impact on the life, body and health of the research subjects.

Likewise, in accordance with the provisions contained in the chapter on "Sanctioning Procedure", as well as in article 247 of the Single Ordered Text of Law No. 27444, Law of Administrative Procedure

General, approved by Supreme Decree No. 004-2019-JUS, (hereinafter, TUO of Law No. 27444), the procedures established in special norms must necessarily observe the principles of the administrative sanctioning power, which are regulated in article 248 of the same legal device, as well as the guarantees of the sanctioning power, as

referring to the aggravating and mitigating criteria of liability, contents in Article 257.

Specifically, one of the principles of sanctioning authority established in Article 248 refers to the "principle of reasonableness," according to which authorities must ensure that committing the punishable conduct is not more advantageous for the offender than complying with the violated rules or accepting the penalty. However, the penalties to be applied must be proportional to the breach classified as an infraction, and the following grading criteria must be observed:

a) The illicit benefit resulting from the commission of the infringement;
b) The probability of detecting the violation;
c) The severity of the damage to the public interest and/or protected legal asset;
d) The economic damage caused;
e) Recidivism, due to the commission of the same infraction within the period of one (1) year from the date the resolution sanctioning the first infraction became final.
f) The circumstances of the commission of the offense; and
g) The existence or not of intentionality in the offender's conduct.

Regarding mitigating factors, Article 257 of the Consolidated Text of Law No. 27444 establishes that these are: a) Express and written acknowledgment of liability at the time the sanctioning procedure is initiated. In cases where the applicable sanction is a fine, this is reduced to an amount not less than half of the fine. b) Others established by special regulations.

Therefore, for the purposes of this Guide on the graduation of the sanctions described above, it is legally feasible to apply both the graduation criteria established in the General Health Law and in the TUO of Law No. 27444.

6. Special Provisions

6.1 General framework of sanctions

6.1.1 Monetary sanctions (Fines)

Initially, the calculation of the "base fine" must consider the illicit profit and the probability of detection. The greater the illicit profit, the greater the expected profit and, therefore, the higher the fine. On the other hand, the lower the probability of detection, the greater the expected profit and, consequently, the higher the fine . 3 The authority may then apply any aggravating and mitigating factors it deems appropriate.

[3] Formally, this result is reached in the following way:

The calculation of this type of fine follows the theory of deterrent fines, seeking to discourage non-compliance.

$$= [\,] \bar{\ddot{y}}\ \ddot{y}$$

Where:

	:	illicitly obtained profit
	:	probability of detection faced by the offender
	:	aggravating and mitigating factors
R		offender recognition factor

6.1.1.1 Illicit profit ( )

Illicit profit refers to the benefit obtained by an agent by breaking a rule or failing to comply with an obligation. These are usually associated with:

- Permanently avoided costs: Corresponds to the savings for the offender generated by not investing the monetary resources necessary to comply with their regulatory or contractual obligations.

- Temporarily avoided costs: This corresponds to the benefit to the offender derived from the use of the economic resources necessary to fulfill their obligations in a lucrative alternative activity for the period of delay in noncompliance. It is equivalent to the "opportunity cost of capital." It is used in cases of temporary noncompliance (untimely fulfillment) of obligations.

- Undue income: corresponds to the increase in income as a result of the identified violation.

$$BE^{NL} = Fine \cdot P_{det} \cdot B^{NL} - (1 - P_{det}) \cdot B^{L}$$

$$BE^{NL} = Fine \cdot P_{det} - B^{NL} \cdot P_{det} + B^{NL} - B^{L}$$

$$BE^{NL} = Fine \cdot P_{det} - B^{NL} \cdot P_{det} + B^{NL} - B^{L}$$

$$(\ ) \quad B^{NL} - Fine \cdot P_{det} \ddot{y} B^{L}$$

$$B_{Ext} \ddot{y} P_{det}$$

$$\frac{B_{Ext}}{P_{det}} \ddot{y} Fine$$

Where:

BENL = Expected benefit from not complying with the law

B^{NL} = Benefit from not complying with the law

B^{L} = Benefit of complying with the law

Pdet = Probability of detection

BExt = Extraordinary profit

6.1.1.2 Probability of detection ( )

The probability of detection refers to the likelihood that the authority will become aware of the commission of an infraction or a breach of contract or regulation by an agent.

In line with the objective of deterring offending behavior, it is important to keep in mind that there is an inverse relationship between the probability of detecting an offense and the incentive to commit it; therefore, a low probability of detection should correspond to a high fine. This element seeks to discourage offending behavior even in situations where potential offenders perceive a low probability of being detected, making it more convenient for them to commit the offense.

The details of the values will be analyzed later.

6.1.1.3 Aggravating and mitigating factors (F)

Factor *F* of the formula seeks to incorporate into the methodology for determining fines all aggravating and mitigating factors provided for in the national legal system, in particular, in the LGS, the Sanctions Regulations and the TUO of Law No. 27444.

The application of the *fn* factors to the calculated base fine will provide the investigating body with the flexibility to adjust the sanction according to the particular circumstances of each case. Thus, the amount of the fine to be imposed on an offending entity may exceed the calculated base fine when more aggravating factors are identified, or it may be reduced when, on the contrary, more mitigating circumstances are identified.

Thus, the aggravating and mitigating factors provided for in the formula will be determined as follows:

$$= 1 + \text{ÿ}_{=1}^{4} = 1 + (1 + {}_2 + {}_3 + 4)$$

The details of the values of *ƒ*n will be analyzed later.

6.1.1.4 Recognition factor ( )

The acknowledgment factor is a mitigating factor when, once an administrative sanctioning procedure has been initiated, the offender expressly acknowledges responsibility in writing. The value of the factor is directly linked to the timeliness of acknowledgment and the degree of recidivism of the offender. That is, the fewer the sanctions, the greater the discount on the penalty due to the acknowledgment factor. In this way, a general incentive is generated to acknowledge and comply with the law (not committing violations).

The details of the *R* values will be analyzed later.

6.1.2 Non-monetary sanctions

As noted, the general objective of sanctions is to deter the agent from engaging in the offending conduct. This is achieved by establishing a consequence for the offending conduct, which may be non-monetary but may still have an effect on the offender that discourages them from engaging in the prohibited action.

Regulations often have non-monetary consequences for offenders, which are usually associated only with statements about their misconduct, such as a warning, or with the deprivation of rights to which offenders are entitled, such as disqualifications,

impediments, closure, cancellation, exposure of the offending conduct in records, actions to disseminate and/or prevent offending conduct, among others.

The regulations impose these types of sanctions under the police authority of the Public Administration and based on the impact on the public interest. However, it has been held that these types of sanctions will only be appropriate to the extent that it is reasonably foreseeable that the restricted activity or private right could lead to the commission of new violations and whenever this could cause serious harm to the public interest.4

As noted, the non-monetary sanctions applicable to the Sponsors, the Contract Research Organization, the research institution, or the principal investigator will be subject to graduation in this Guide.

6.2 Practical application in the context of clinical trials

6.2.1 Monetary sanctions (Fines)

As previously noted, the base fine requires identifying the illicit benefit obtained by the offender and establishing the value of the probability of detection.

6.2.1.1 Illicit profit

In the present case, based on the available information5 , an approximation will be provided to the illicit benefit obtained by the offender based on: i) 80% of the Study Budget in Peru (Report - REPEC), the *"Overhead"* recorded
in the Detailed National Total Clinical Trial Budget Form (FOR-GITT-32) and the income obtained by the Principal Investigator derived from the Clinical Trial.

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4 SANTAMARÍA PASTOR, Juan Alfonso. *Principles of General Administrative Law.* IUSTEL Publishing House, Second Edition, 2009, Madrid, p. 411.

5 The National Institute of Health provided data reports from the Peruvian Registry of Clinical Trials - REPEC from 2015 to 2022.

6.2.1.1.1 Sponsors and Research Organization by Contract

With respect to the Sponsor (or the Contract Research Organization –
OIC) the benefit is directly related to the results obtained in clinical trials, which represent an investment on which a return is expected.

Indeed, organizations invest in Research and Development (R&D) to develop new or improved products or processes. The amounts allocated to R&D represent an investment for organizations, as they will be recovered over time, either through the product or process being researched, or through others that benefit from the knowledge and experience acquired as a result of the first.

In this sense, it is possible to associate the benefits obtained by the sponsors (or the OIC) to the investment made for the clinical trial in Peru.
(Study Budget in Peru), since it is expected that the income obtained subsequently will exceed said investment, so a profit is expected to be obtained.

Although the benefits are directly associated with the investment, it is important to establish a rate of return on that investment that can be understood as a benefit. In the case of clinical trials conducted in Peru, these are usually a small part of a larger set of clinical trials.
, so proportionally the investment made in Peru would represent a smaller part of a larger investment. Therefore, any rate of return established based on the investment in Peru will be diminished if the total investment in clinical trials is considered; and it will be even lower if the investment in clinical trials (in Peru or abroad) represents only a part of the total investment required to obtain better products or services.

In this sense, the illicit benefit ( ) for the base fine of the sponsors (or the OIC) will be determined on the basis of 80% of the Study Budget in Peru according to the considerations in Annex 1 of this Guide.

6.1.2.1.2 Research institution

For the research institution, the benefit is related to the overhead that the institution itself receives directly for its participation in the clinical trial.

Indeed, according to the Detailed National Total Clinical Trial Budget Form (FOR-GITT-32), the research institution receives an overhead benefit for its participation in the clinical trial that may result in illicit profit ( ) if it is responsible for a violation of the regulations.

Consequently, the value of the illicit benefit ***(B)*** for the research institution will be associated with the value of the overhead recorded in the Detailed National Total Clinical Trial Budget Form (FOR-GITT-32).

[6] 7.01% considering the number of participants in Peru and abroad from 2014 to 2022 (REPEC source).

6.1.2.1.3 Principal Investigator

In relation to the Principal Investigator, the benefit is directly related to the income received for participation in the Clinical Trial regardless of the origin
of the income.

Participation in a clinical trial typically generates income for the Principal Investigator, which is used to determine the illicit benefit ***(B)*** from the offending conduct; therefore, such income must be considered when calculating the fine.

6.2.1.2 Probability of detection

Detection probability values are usually associated with the Public Administration's experience in detecting infringing behavior. Generally, predetermined values are established, associated with criteria identified by the Administration that may facilitate or hinder the detection of infringing behavior. Thus, when the established criteria reveal circumstances that facilitate the detection of infringing behavior, these criteria should be associated with the highest probability; otherwise, they should be associated with a lower probability.

Thus, based on this experience, and in order to reduce the discretion of officials to assign a value to the probability of detection in particular cases, three probability scenarios and respective values are proposed: **high, medium, low,** which are characterized by objective criteria, according to the details shown below:

Table 1
Probability of detecting the violation

Probability	Worth	Criterion
High	100%	• When the officer self-reports the violation; or • When the violation is detected through ordinary supervisory procedures; or • When the violation is detected by information sent periodically.
Average	50%	• When the violation is detected via Reports/complaints from users or third parties; and are not covered by ordinary supervisory procedures or periodically submitted information.
Low	20%	• When the violation is detected by unscheduled supervisory activities.

6.2.1.3 Aggravating and mitigating factors (F)

Determining the illicit profit and the probability of detection allows for calculating the “base fine” to be imposed.

To this result, the mitigating and aggravating factors, known as the F factor, must subsequently be calculated. These factors are directly related to the offender's conduct. This F factor is intended to increase (aggravating factors) or decrease (mitigating factors) the amount of the base fine.

The determination of these circumstances is part of the background of the authority in relation to the matter, as well as the evidence collected during the monitoring carried out to ensure compliance with the obligations and the conduct attributable to the offenders.

The inclusion of this factor in the formulas will allow the investigating body to adjust the fine according to the circumstances and particular conduct of the provider in each case.

In the absence of any aggravating or mitigating circumstances, the F factor is equal to one (F = 1 or 100%).

These mitigating and aggravating factors are defined in articles 248 and 257 of the TUO of Law No. 27444, as well as in article 135 of the LGS, as described in numeral C of section 5.2 of this Guide.

In the present case, the following aggravating and mitigating circumstances have been included:

1. **Damage caused or potential damage to the life, body and health of persons (public interest and/or protected legal asset):** in accordance with the provisions of article 135 of the LGS, article 3 of the Sanctions Regulations and literal c) of section 3 of article 248 of the TUO of Law No. 27444.

2. **Recidivism:** in accordance with the provisions of article 135 of the LGS and literal e) of section 3 of article 248 of the TUO of Law No. 27444.
3. **Circumstances of the commission of the infraction:** in accordance with the provisions of article 135 of the LGS and literal f) of section 3 of article 248 of the TUO of Law No. 27444.

4. **Intentionality:** in accordance with the provisions of literal g) of section 3 of the Article 248 of the TUO of Law No. 27444.

The **F** factor is equivalent to the sum of all the individual values assigned to each factor *fn,* depending on the circumstances that could be observed in each particular case, as shown in the following table:

Table 2

Aggravating and mitigating factors

F	Factors	Assessment
f1	**Damage caused or potential damage to the life, body and health of people**	
	It potentially affects people's health	0.25
	It affects people's health in real ways	0.50
f2	**Recidivism**	
	First recurrence of the same offense	0.25
	Two or more repeat offenses of the same offense	0.30
f3	**Circumstances of commission of the offense**	

	Aggravating factors	
	Obstructing the action of the authorities	0.15
	Committing the offense to hide another	0.10
	Avoiding responsibility or attributing it to others or other aggravating circumstances	0.10
	Mitigating circumstances	
	Mitigation of damage, before notification of impeachment of charges	-0.40
	Mitigation of damage, before the first instance resolution	-0.15
f4	**Intentionality**	
	Intentionality	0.35

If aggravating or mitigating circumstances (fn) are found, the percentage by which each mitigating and/or aggravating circumstance decreases and/or increases, respectively, the base fine must be established. To do this, all percentages (fn) must be added together and the unit (or 100%) added. This can be done using the following expression:

$$= 1 + \ddot{y} = 1 + (1 \quad + \quad _2 + \quad _3 + 4) \qquad \text{(4, =1)}$$

To do this, taking into account the particularities of each case, an individual evaluation of each aggravating or mitigating factor provided for in the table above (fn) must be carried out to add it and form the final factor F.

When applying aggravating and mitigating factors, the possibility of their occurrence in an exclusive and/or concurrent manner must be considered.

6.2.1.4 Express recognition

As noted, the acknowledgment factor is applied as a mitigating factor when, once an administrative sanctioning procedure has been initiated, the offender expressly acknowledges responsibility in writing. In the present case, the following characteristics were included in the application of this factor:

- Period 1: From the notification of the charge made by the authority until the date on which the deadline for the administration to present its defense expires.

- Period 2: From the day after the end of Period 1 until fifteen (15) calendar days after said Period.
- Period 3: From the day after the end of Period 2 until the date of submission of the discharges regarding the investigation report.

In cases where the first violation is being acknowledged, the fine may be reduced by up to half, depending on the timing of the admission. Furthermore, the reduction will be smaller depending on the individual's previous sanctions.

Thus, the R factor (which multiplies the value of the base fine) will adopt the following values, depending on both the number of violations committed by the administrator as provided for in the Regulation, and the opportunity in which they present their recognition.

Table 3

Recognition Factor *(R)*

Graduation	Number of violations		
			3 or more
Period 1	1	2	0.70
Period 2	0.50	0.60	0.80
Period 3	0.60 0.70	0.70 0.80	0.90

6.2.2 Non-monetary sanctions

6.2.2.1 Sponsors and/or Research Organization by Contract

In those minor level of severity infractions **where the calculation of the fine is less than 0.5 UIT,** a warning will be issued, and registration and publication on a list of offenders that the DIIS will prepare and publish in accordance with current applicable regulations.

Likewise, in those infractions of serious severity level where the calculation of the fine is greater than 100 UIT and three (3) or more aggravating factors of the Aggravating and Mitigating Factors (F) are met, the cancellation of the clinical trial will be applicable, and the registration and publication in a list of offenders that the DIIS will prepare and publish in accordance with the applicable regulations in force.

Finally, in those violations of very serious severity level where the calculation of the fine is greater than 100 UIT and two (2) or more aggravating factors of the Aggravating and Mitigating Factors (F) are met, the cancellation of the clinical trial will be required, and the registration and publication in a list of offenders that the DIIS will prepare and publish in accordance with the applicable regulations in force.

6.2.2.2 Research Institution

For minor offenses **where the fine is less than 0.5 UIT, a warning will be issued,** along with registration and publication on a list of offenders that the DIIS will prepare and publish in accordance with current applicable regulations.

Likewise, in those infractions of serious severity level where the calculation of the fine is greater than 100 UIT and three (3) or more aggravating factors of the Aggravating and Mitigating Factors (F) are met, the closure of a research center for a clinical trial will be required, and the registration and publication in a list of offenders that the DIIS will prepare and publish in accordance with the applicable regulations in force.

Finally, in those infractions of very serious severity level where the calculation of the fine is greater than 100 UIT and two (2) or more aggravating factors of the Aggravating and Mitigating Factors (F) are met, the cancellation of the registration will be applicable.

of the research center, and the registration and publication in a list of offenders that the DIIS will prepare and publish in accordance with the applicable regulations in force.

6.2.2.3 Principal Investigator

For minor offenses **where the fine is less than 0.5 UIT, a warning will be issued,** along with registration and publication on a list of offenders that the DIIS will prepare and publish in accordance with current applicable regulations.

Likewise, in those infractions of serious severity level where the calculation of the fine is greater than 100 UIT and three (3) or more aggravating factors of the Aggravating and Mitigating Factors (F) are met, the researcher will be restricted from carrying out future trials for up to a period of three (03) years according to the considerations of the Annex, and the registration and publication in a list of offenders that the DIIS will prepare and publish in accordance with the applicable regulations in force.

Finally, in those violations of very serious severity level where the calculation of the fine is greater than 100 UIT and two (2) or more aggravating factors of the Aggravating and Mitigating Factors (F) are met, the researcher will be restricted from carrying out future trials for up to a period of five (05) years according to the considerations of the Annex, and the registration and publication in a list of offenders that the DIIS will prepare and publish in accordance with the applicable regulations in force.

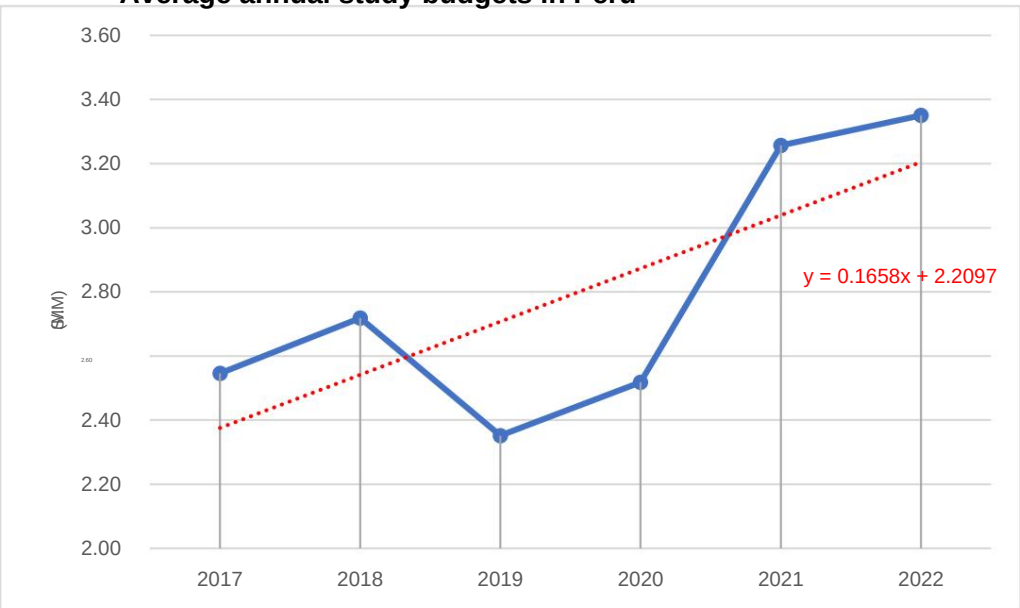
Annex 1. Calculation of the Monetary Sanction

1. Sponsors and Contract Research Organization

For the purpose of calculating the monetary penalty, two factors must be considered: first, the law establishes ranges for penalties based on the severity of the violation, and second, clinical trial budgets in Peru tend to increase over time.

Indeed, Section 3.3 of Article 3 of the Sanctions Regulation establishes that fines will range from 0.5 to 20 UITs for minor violations, from 21 to 60 UITs for serious violations, and from 61 to 100 UITs for very serious violations. The following graph shows the annual average of clinical trial budgets authorized in Peru, and demonstrates a growing and fluctuating trend over the years.

Chart 1
Average annual study budgets in Peru



Note 1: The positive value associated with the variable "x" in the trend equation shows growth over time.

Note 2: rounded values
Source: REPEC

The identified situations combined indicate that over time, illicit profits would tend toward the maximum limits established by the law. In this regard, it is proposed to align the average study budget in Peru with the average fine range established by the law, based on severity. Thus, a clinical trial with an average study budget in Peru would be subject to the midpoint of the fine range established by the law, based on severity (i.e., 10 UITs for minor violations, 40 UITs for serious violations, and 80 UITs for very serious violations).

[7] The annual average considers 90% of the available centered data in order to avoid the influence of anomalous values *(outliers)* that influence the results.

Table 4

Average value of the fine range

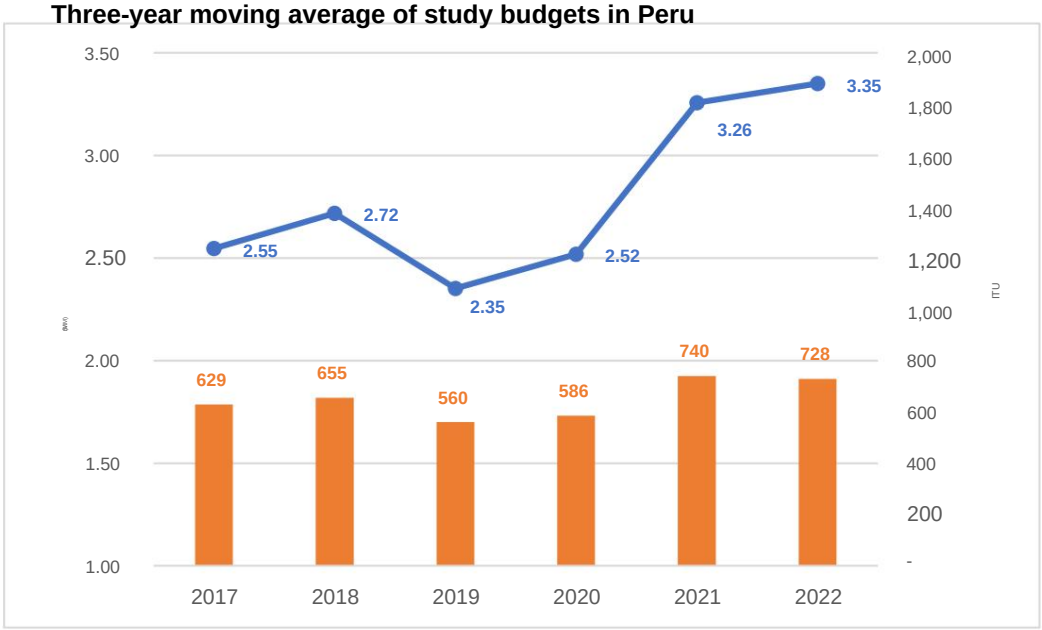
Gravity	ITU
Mild	10
Serious	40
Very serious	80

A contingency associated with this proposal is that the average may vary due to the presence of annual anomalous values or the annual context of the development of the clinical trial outside the clinical trial itself. In this sense, in order to favor predictability and stabilize the average, it is proposed to consider a three (3) year moving average, that is, the average for a particular year will use the data from that year and also from the previous 2 years; likewise, it is proposed to center the data set to be used for the annual average at 90%, that is, for a particular annual average, with respect to the total data available for the three (3) years, the 5% of the data with the lowest values and the 5% of the data with the highest values will not be used.

The following graph, taking into account the aforementioned considerations, shows the average annual values of study budgets in Peru.

Chart 2

Three-year moving average of study budgets in Peru



Note: rounded values
Source: REPEC

As shown, according to the adopted considerations, the moving annual average of budgets in Peru is greater than 550 UITs in all cases over the last six years, even reaching an average value greater than 700 UITs. Thus, considering that the moving average value for each year corresponds to the average fine range established by the Regulations on Sanctions according to severity (i.e., 10 UITs for minor infractions, 40 UITs for serious infractions, and 80 UITs for very serious infractions) implies that, in all cases, the rate of illicit profit on the investment is less than 9%; it would be even lower if one considers that clinical trial investment in Peru represents a smaller portion of the investment in clinical trials in general compared to other countries.

Consequently, the value of the illicit benefit ***(B)*** for the sponsor (or the CRO) will be associated with the average annual moving value of clinical trial budgets in Peru, for the year of the infringement or the immediately preceding year (depending on the availability of information); the illicit benefit ***(B)*** will be valued at 10 UITs for minor infringements, 40 UITs for serious infringements, and 80 UITs for very serious infringements, if it is within the average annual moving value, or a proportional higher or lower percentage, depending on whether the budget in Peru for the clinical trial in question is below or above the average annual value of clinical trial budgets in Peru, respecting the limits established for each type of infringement according to its severity.

2. **Non-monetary sanctions**

Principal Investigator

In addition to any illicit profit that may be obtained, the consequences of a principal investigator's misconduct are directly related to the participants (research subjects) in clinical trials, as well as to the clinical trial's own objectives.

Indeed, participants are subjects who place their trust in the clinical trial's potential for immediate or subsequent improvement for themselves or other subjects affected by the diseases being investigated. Therefore, misconduct by the principal investigator that affects the normal conduct of the clinical study violates the trust participants place in its proper conduct; therefore, their number should be considered when determining the sanction.

Clinical trials, on the other hand, seek to identify or establish improved products or procedures associated with specific diseases. In this sense, the misconduct of a principal investigator in a clinical trial jeopardizes or eliminates the development of improved products or procedures that can cure, reduce, or control the diseases under investigation. Thus, the sanction must be linked to the type of disease under investigation, since the investigator's misconduct hinders or prevents the achievement of the clinical trial objectives for the well-being of individuals.

In the present case, a sanction proposal will be provided to the principal investigator, during which period he/she will be restricted from conducting future clinical trials ***(non*** -monetary sanction), based on the available information, considering i) the minimum and maximum sanction period (depending on severity), ii) the number of participants in Peru in clinical trials8 and iii) the ranking of the main causes of death recorded by the National Computer System of Deaths - SINADEF9 .

In this regard, the principal investigator will be restricted from conducting future clinical trials for a period ***(Per)*** equivalent to half of the maximum possible sanction period based on the severity (18 months for serious violations and 48 months for very serious violations), when the number of participants in the clinical trial affected by the violation is within the average number of clinical trial participants in Peru; or a proportional percentage, as appropriate.

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8 The National Institute of Health provided data reports from the Peruvian Registry of Clinical Trials - REPEC from 1996 to 2022, with partially completed information on the items included in the reports.

9 More information : http://www.minsa.gob.pe/reunis/data/defunciones_causas_principales.asp

Table 5

Half of the maximum possible sanction period

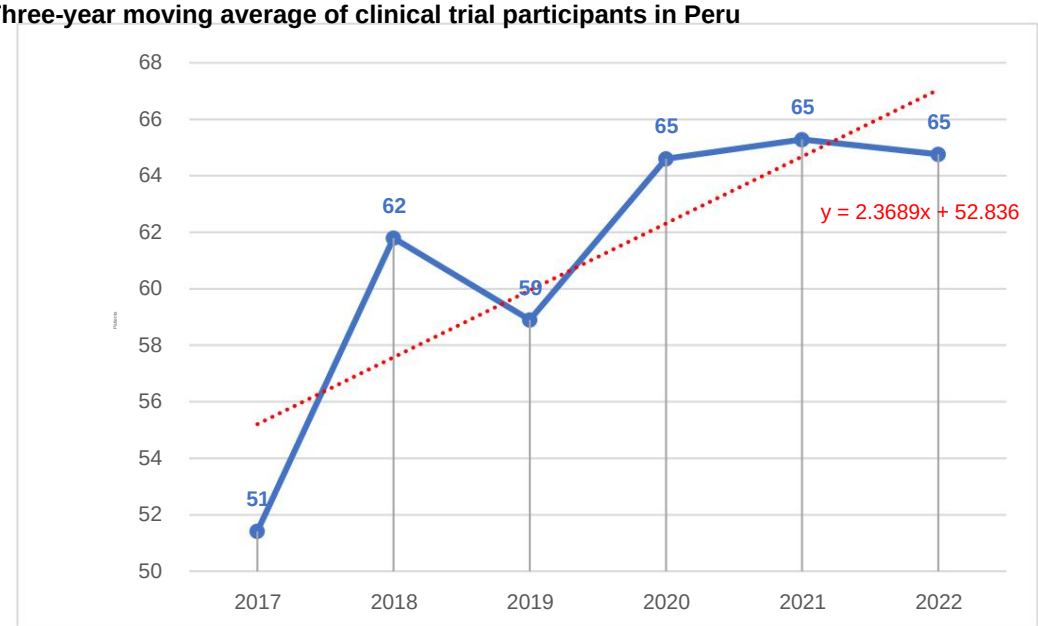
Gravity	Months
Mild	Not applicable
Serious	18
Very serious	48

A contingency associated with this proposal is that the average may vary due to the presence of annual anomalous values or the annual context of the clinical trial development outside the clinical trial itself. In this sense, in order to promote predictability and stabilize the average, it is proposed to consider a three (3) year moving average, that is, the average for a particular year will use the data from that year and also from the previous 2 years; likewise, it is proposed to center the data set to be used for the annual average at 90%, that is,
For a particular annual average, with respect to the total data available for the three (3) years, neither the 5% of the data with the lowest values nor the 5% of the data with the highest values will be used.

The following graph, taking into account the aforementioned considerations, shows the average annual rates of clinical trial participants in Peru.

Chart 3

Three-year moving average of clinical trial participants in Peru



Note: rounded values
Source: REPEC

As shown, the moving annual average of clinical trial participants in Peru ranges between 51 and 64 participants in the last 6 years.

Likewise, the period during which the principal investigator will be restricted from conducting future clinical trials ***(Per)*** must be directly associated with the types of diseases under study in the clinical trial ***(TE)*** and aggravating and mitigating factors (F).
For this purpose, the period ***(Per)*** must be multiplied by a factor that considers the percentage share of the sum of diseases subject to study according to the SINADEF publication ***(TE),*** of the year of the violation or the immediately preceding year, depending on the availability of information.

Where:

$$= 1 + \ddot{y} = \underset{=1}{1} + (1 \quad + \quad {}_{2} + \ddot{y} +)$$

It is the annual participation as a cause of death according to SINADEF publication, of the year of the violation or the immediately preceding year, according to available information.

And the mitigating and aggravating circumstances of the particular case

Table 6

Aggravating and mitigating factors

F	Factors	Assessment
f1	**Recidivism**	
	First recurrence of the same offense	0.25
	Two or more repeat offenses of the same offense	0.30
f2	**Circumstances of commission of the offense**	
	Aggravating factors	
	Obstructing the action of the authorities	0.15
	Committing the offense to hide another	0.10
	Avoiding responsibility or attributing it to others or other aggravating circumstances	0.10
	Mitigating circumstances	
	Mitigation of damage, before notification of impeachment of charges	-0.40
	Mitigation of damage, before the first instance resolution	-0.15
f3	**Intentionality**	
	Intentionality	0.35

Thus, the aggravating and mitigating factors provided for in the formula will be determined as follows:

$$= 1 + \ddot{y} = \underset{=1}{1} + (1 \quad + \quad {}_{2} + 3)$$

Consequently, the penalty according to severity will be determined by:

$$\text{Penalty (year and months)} = Per \times TE \times F$$

It is recommended that in cases where the information for a monetary sanction does not convince the authority, they opt for a non-monetary sanction based on the aforementioned considerations.

3. Application examples

The examples below are for illustrative purposes only, i.e., they have been provided for reference purposes only and are examples only, using fictitious data that has no binding effect on the entity.

3.1. Monetary Sanctions

a. Sponsors and Contract Research Organization

Initial conditions:

- Clinical Trial Budget: S/ 500,000.00
- 80% of the clinical trial budget: S/ 400,000.00
- Year of the violation: 2022
- Severity: Severe

Calculation:

Sponsor and OIC			Fountain
80% Budget in S/.	400,000.00	TO	REPEC Information
ITU value (year)	5,150.00	B	Sunat https://www.sunat.gob.pe/indicestasas/uit.html
Budget in ITU	77.67 C=A/B		
Annual Average (year)	728 D		According to considerations in Chart 2 of the Guide
The case (Budget in ITU) % of the	77.67	C	
case on the average	10.67% E=C/D		
ITU range average	40	F	According to considerations in Table 4 of the Guide
% of the case above the average	10.67%	AND	
Illicit benefit UIT	4.3 G=FxE		
Probability	0.2	H	According to considerations in Table 1 of the Guide
Base fine	21.3 I=G/H		
F Factor *	1.4	J	According to considerations in Table 2 of the Guide
R Factor **	1.0	K	According to considerations in Table 3 of the Guide
Final UIT fine	**29.87** L=IxJxK		Consider the limits according to severity of Article 3.3 of the DS 018-2023-SA

*
**Note: if F is not used, 1 is used, otherwise F = 1 + SUM of "f".
Note: if R is not used, set to 1, otherwise, set to the chosen value.

b. Research institution

Initial conditions:

- Overhead: S/ 100,000.00
- Year of the violation: 2020
- Severity: Very Serious

Calculation:

Research institution		**Fountain**	
Overhead in S/.	100,000.00	TO	Detailed National Total Clinical Trial Budget Form (FOR-GITT-32)
ITU value (year)	5,150	B	Sunat https://www.sunat.gob.pe/indicestasas/uit.html
Overhead at ITU	19.42	C=A/B	
Probability	0.5	D	According to considerations in Table 1 of the Guide
Base fine	38.8	E=C/D	
F Factor *	1.5	F	According to considerations in Table 2 of the Guide
R Factor **	0.9	G	According to considerations in Table 3 of the Guide
Final UIT fine	**52.43**	H=ExFxG	Consider the limits according to severity of Article 3.3 of the DS 018-2023-SA

*
**Note: if F is not used, 1 is used, otherwise F = 1 + SUM of "f".
Note: if R is not used, set to 1, otherwise, set to the chosen value.

c. Principal Investigator

Initial conditions:

- Income: S/ 80,000.00
- Year of the violation: 2021
- Severity: Mild

Calculation:

Principal Investigator			Fountain
Income in S/.	80,000.00	TO	Income received for your participation in the Clinical Trial regardless of the source of income
ITU value (year)	5,150.00	B	Sunat https://www.sunat.gob.pe/indicestasas/uit.html
Admission to ITU	15.53 C=A/B		
Probability	1.0	D	According to considerations in Table 1 of the Guide
Base fine	15.53 E=C/D		
F Factor *	1.0	F	According to considerations in Table 2 of the Guide
R Factor **	0.7	G	According to considerations in Table 3 of the Guide
Final UIT fine	**10.87** H=ExFxG		Consider the limits according to severity of Article 3.3 of the DS 018-2023-SA

* Note: if F is not used, 1 is used, otherwise F = 1 + SUM of "f".

** Note: if R is not used, set to 1, otherwise, set to the chosen value.

3.2 Non-Monetary Sanctions

a. Principal Investigator

Initial conditions:

- Number of EC patients: 80
- Year of the violation: 2021
- Severity: Severe

Calculation:

Principal Investigator		Fountain	
Number of patients in the EC	80	TO	REPEC Information
Annual Average (year)	65	B	According to considerations in Chart 3 of the Guide
The case (Number) %	80	TO	
of the case above the average	123.08% C=A/B		
Average range months	18	D	According to considerations in Table 5 of the Guide
% of the case above the average	123.08%	C	
Base months	22.2 E=DxC		
TE Factor *	1.128	F	SINADEF and considerations of the Guide
Factor F**	1.1	G	According to considerations in Table 6 of the Guide
Months of Suspension	**27** H=ExFxG		Consider the limits according to severity of Article 3.3 of the DS 018-2023-SA

* Note: if TE is not used, set to 1, otherwise TE = 1 + SUM of "te".
http://www.minsa.gob.pe/reunis/data/defunciones_causas_principales.asp

** Note: if F is not used, 1 is used, otherwise F = 1 + SUM of "f".