Association for the Accreditation
of Human Research Protection Programs, Inc.®

ADDENDUM

The Kingdom of Spain

General Comments

The Kingdom of Spain ("Spain") *Addendum* to the *Evaluation Instrument for Accreditation* ("*Evaluation Instrumen*t") is intended for use by organizations in Spain seeking accreditation, by peer reviewers evaluating organizations in Spain, and by accredited organizations in the US that conduct or oversee research in Spain. This *Addendum* includes Standards and Elements where Spain's law, regulations, and guidelines require significant additional protections beyond those defined in the *Evaluation Instrument* or are significantly different from requirements in the *Evaluation Instrument* and is intended to be used in conjunction with the *Evaluation Instrument*. The *Addendum* focuses on the laws most relevant to human research protection programs, including research ethics committees. However, it is not an exhaustive account of all requirements covering research involving human participants in Spain.

The Addendum is based on a review of the laws, policies, and guidance of Spain and the European Union, the most relevant of which are:

- EU Implementing Regulation No. 536/2014 Clinical Trials on Medicinal Products for Human Use (CTR)
- EU Clinical Trials on Medicinal Products 2004/27
- EU Regulation No. 2017/745 on Medical Devices (MDR), adopted in Spain as Royal Decree 1345/2007
- EU Medical Device Directives 90/385/EEC or 93/42/EEC
- ICH-GCP(E6)(R2) – As of March 2025, Spain follows (R2)
- Oviedo Convention on Human Rights and Biomedicine
- Royal Decree 1015/2009, of 19 June, Regulating Clinical Trials with Medicinal Products, Ethics Committees for Investigation with Medicinal Products and the Spanish Clinical Studies Registry
- Royal Decree 192/2023, of March 21 Regulating medical devices.
- Act 41/2002, of 14 November, regulating patient autonomy and rights and obligations in terms of clinical documentation and information.
- Royal Decree 957/2020, of November 3, which regulates observational studies with medicines for human use.
- Royal Decree 1716/2011, of 18 November, which establishes the basic requirements for authorization and operation of biobanks for biomedical research purposes and the processing of human biological samples, and regulates the operation and organization of the National Registry of Biobanks for biomedical research, particularly with regard to the relevant sections of informed consent and possible documents for transfer of biological materials

The laws of Spain describe requirements for oversight of research, including review by a research ethics committee (Comités de Ética de la Investigación) or "CEI". CEIs fall under the authority of the Spanish Agency of Medicines and Medical Devices (Agencia Española de Medicamentos y Productos Sanitarios; AEMPS). CEIs review a broad range of research, including non-interventional research, non-commercial research, and research not covered by the EU clinical trial regulations.

Spain is also part of the EU and follows EU regulations when studies require coordination of ethics and regulatory reviews among different member states, while allowing local context issues to be assessed by each member state. This framework is described in the EU Clinical Trial Regulation (CTR) and EU Medical Device Regulation (MDR), which govern certain clinical studies conducted in the EU and describe the process for regulatory and ethics review. As with other member states, Spain's laws describe the process for coordinating oversight by AEMPS with the RMS and specifies requirements for local ethics review.

For certain research involving drugs, the CTR specifies that to obtain an authorization to conduct a clinical study, the sponsor (an individual, company, institution or organization which takes responsibility for the initiation, management and setting up the financing of the clinical trial) must submit an application dossier to the intended member states concerned through the EU European Portal and Database, instead of applying separately to each member state. For research involving devices, the MDR describes a similar process, but there are other pathways for device approval. Sponsors applying to EU member states for marketing applications propose one member state to serve as the reporting member state (RMS) responsible for coordinating regulatory and ethics review and serving as the point of contact for the sponsor. There is a two-part review.

- In Part I of the review, the reporting member state (RMS) is responsible for assessing the anticipated therapeutic and public health benefits; the risks and inconveniences for the subject; compliance with requirements for manufacturing and import of investigational medicinal products and auxiliary medicinal products; labelling requirements, and the investigator brochure. The RMS issues its assessment, and coordinates comments by member states. A member state may refuse to authorize a clinical trial if it disagrees with the conclusion of the RMS, under limited conditions, such as a determination that participation in the clinical trial would lead to a participant receiving an inferior treatment than in normal clinical practice in the member state. AEMPS is responsible for coordinating member state reviews for clinical trials governed by EU CTR and EU MDR regulations.
- In Part II of the review, which may occur concurrently, each member state concerned must assess the application, in its own territory, to determine compliance with the member state's laws, regulations and other requirements governing the consent process and consent document; participant compensation; suitability of researchers and research sites; privacy; insurance; and management of biological samples. If the ethics committee designated to review the study in the member state issues a negative opinion, after an appeals process, then that opinion is governing for the member state. AEMPS is responsible for coordinating member state reviews for clinical trials governed by EU CTR and EU MDR regulations.

In contrast to the research ethics committee (Comités de Ética de la Investigación) or "CEI" noted above, review of clinical trials that fall under EU CTR and EU MDR regulations must be reviewed by an Ethics Committee for investigation with medicinal products (Comités de Ética de la Investigación con medicamentos), or CEIm, which are accredited by the Spanish Agency of Medicines and Medical Devices (AEMPS). The CEIm are a subset of all the CEIs and are accredited by the Spanish Agency of Medicines and Medical Devices as a condition of being authorized to review clinical trials covered by the EU CTR or EU MDR. (Royal Decree 1090/2015, Article 13)

In summary, organizations can either:

- Serve as a reviewing CEI for non-interventional research, or non-commercial research, or research not otherwise covered by the EU CTR or EU MDR.
- Serve as the designated CEIm for Part I of review, if recognized by AEMPS to serve as a CEIm.
- Rely upon a designated CEIm for research covered by the EU CTR and EU MTR regulations, while also conducting their own Part II review, and coordinate their review with the Spanish.

For purposes of this Addendum, CEI and CEIm are both referred to below as "IRBs/ECs".

Spain's regulatory system incorporates good clinical practice, currently (R2), and AAHRPP evaluates organizations in Spain to ensure requirements of ICH-GCP (E6)(R2) are included in written materials.

This Addendum is AAHRPP's current understanding of additional requirements covering organizations conducting or reviewing research in Spain.

We appreciate questions, concerns, and suggestions to improve this document. Please email accreditation@aahrpp.org.

Domain I: Organization

Standard I-1: The organization has a systematic and comprehensive Human Research Protection Program that affords protections for all research participants. Individuals within the organization are knowledgeable bout and follow the policies and procedures of the Human Research Protection Program.

Element I.1.A. The Organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.

Policies define clinical studies, clinical trials, and low intervention clinical trials, non-interventional studies, and observational studies with medications. (EU CTR Article 2, 1-4; Royal Decree 1090/2015, Article 2; Royal Decree 957/2020)

- Clinical study means any investigation in relation to humans intended:

    - To discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products.
    - To identify any adverse reactions to one or more medicinal products; or
    - To study the absorption, distribution, metabolism and excretion of one or more medicinal products with the objective of ascertaining the safety and/or efficacy of those medicinal products.
- Clinical trial means a clinical study which fulfils any of the following conditions:
    - The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the member state concerned.
    - The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or
    - Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.
- Low-intervention clinical trial means a clinical trial which fulfils the following conditions:
    - The investigational medicinal products, excluding placebos, are authorized.
    - According to the protocol of the clinical trial:
        - The investigational medicinal products are used in accordance with the terms of the marketing authorization; or
        - The use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the member states concerned; and
    - The additional diagnostic or monitoring procedures do not pose more than a minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any member state concerned.
- Observational study with medications means any investigation that involves the collection of individual data related to the health of people, provided that it does not meet any of the conditions required to be considered a clinical trial and is carried out for one or more of the following purposes:
    - Determine the beneficial effects of medications, as well as their modifying factors, including the perspective of patients, and their relationship with the resources used to achieve them.
    - Identify, characterize or quantify the adverse reactions of medications and other risks to the safety of patients related to their use, including possible risk factors or effect modifiers, as well as measuring the effectiveness of management measures. risks.
    - Obtain information on the patterns of use of medications in the population.

    - Observational drug studies should aim to complement the already known information on the drug without interfering with routine clinical practice.
- Non-interventional study means a clinical study other than a clinical trial.
- Non-commercial clinical research means a clinical study with the following characteristics (Royal Decree 1090/2015, Article 2):
    - The sponsor is a university, hospital, public scientific organization, non-profit institution, patient organization or individual investigator.
    - The ownership of the investigation data belongs to the sponsor from the inception of the study.
    - There are no agreements between the sponsor and third parties that allow them to use the data for regulatory or marketing purposes.
    - The design, conduct, recruitment, recording of data and reporting of the results of the investigation remains under the control of the sponsor.
    - Given their characteristics, these studies cannot be part of the development program for marketing authorization of a medicinal product.

Policies and procedures should define when other activities are considered research involving human participants as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge, or an equivalent definition (e.g., research other than clinical studies, such as studies involving patient data).

Element I.1.D. The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.

Policies specify that clinical studies and other research should be conducted in accordance with the ethical principles in the:

- Declaration of Helsinki
- Oviedo Convention on Human Rights and Biomedicine
- International Convention on the Rights of People with Disabilities as adopted in Act 26/2011, of 1 August

Policies specify that the rights, safety, human dignity, and well-being of the subjects prevail over any other interest. (Royal Decree 1090/2015, Article 3; Act 14/2007, Article 2)

Element I.1.F. The organization has and follows written policies and procedures for reviewing the scientific or scholarly validity of a

proposed research study. Such procedures are coordinated with the ethics review process.

Policies and procedures specify that when evaluating scientific or scholarly validity the IRB/EC considers the available nonclinical and clinical information on an investigational product is adequate to support the proposed clinical trial. (ICH-GCP)(E6)(R2)

Standard I-6: The Organization has and follows written policies and procedures to ensure that research is conducted so that financial conflicts of interest are identified, managed, and minimized or eliminated.

Element I.6.B. The Organization has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of researchers and research staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The Organization works with the Institutional Review Board or Ethics Committee in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate.

When serving as the designated ethics committee for clinical studies covered by the CTR or MDR or relying upon an external ethics committee for studies covered by the CTR or MDR:

- Researchers must complete the Declaration of Interest Template developed and endorsed by the EU Clinical Trials Expert Group to comply with the CTR and MDR.

When relying upon a designated ethics committee at another organization for clinical studies covered by the CTR or MDR:

- Policies should describe how the organization will identify financial interests of research staff internally.
- If the organization identifies a financial conflict of interest to staff, policies should describe the process of managing financial conflicts of interest to staff.

For other research, policies should describe the process for identifying, reviewing, and managing financial interests of researchers and research staff.

Standard I-7: The organization has and follows written policies and procedures to ensure that the use of any investigational or unlicensed test article complies with all applicable legal and regulatory requirements.

Element I.7.A. When research involves investigational or unlicensed test articles, the organization confirms that the test articles have

appropriate regulatory approval or meet exemptions for such approval.

AAHRPP evaluates organizations outside the US based on country-specific laws and/or ICH-GCP (E6). Organizations outside the US are generally not required to follow US FDA requirements, provided they follow country-specific law and country-specific GCP or follow ICH-GCP (E6).

AAHRPP will generally not evaluate organizations outside the US for compliance with US FDA requirements, and organizations can substitute information in this Addendum for US FDA requirements for this Element in the *Evaluation Instrument.*

Policies define medicinal products for human use and medical devices. (Royal Decree 1015/2009, Article 2).

- A medical product for human use is any substance or combination of substances presented as having properties for treating or preventing disease in human beings or which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.
- A medical device is any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by their manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
    - Diagnosis, prevention, monitoring, treatment or alleviation of a disease.
    - Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap.
    - Investigation, replacement or modification of the anatomy or of a physiological process.
    - Control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Clinical trials with medicinal products in Spain must have prior authorization from the Spanish Agency of Medicines and Medical Devices (AEMPS) after a scientific and ethical assessment of Parts I and II, including:

- The favorable opinion issued by an IRB/EC (CEIm) in Spain.
- The decision for authorization by the Spanish Agency of Medicines and Medical Devices (AEMPS).
- The agreement of the participating site management which shall be expressed by the signing of the contract between the sponsor and organization conducting the research.
    - Only in clinical trials in which the sponsor/investigator belongs to the site and signing of the contract is not required shall the express agreement of the participating site management be required.

- No clinical trials with gene therapy medicinal products which result in modifications to the subject's germ line genetic identity may be conducted.

Policies and procedures specify that IRB/EC approval is required prior to the start of research involving a medical device. (Royal Decree 192/2023, Article 30)

Element I.7.B. The organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.

Policies and procedures describe handling and control of investigational products (ICH-GCP)(E6)(R2):

- Where allowed or required, the researcher may assign duties for investigational articles accountability at the trial sites to an appropriate pharmacist or another appropriate individual who is under the supervision of the researcher.
- The researcher, pharmacist, or other designated individuals will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial participants.
- Researchers should maintain records that document adequately that the participants are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

If the researcher serves as a sponsor-investigator (ICH-GCP)(E6)(R2):

- The researcher is responsible for ensuring manufacturing, handling, and storage in accordance with applicable good manufacturing practice.

Policies and procedures describe control of devices (Royal Decree 192/2023)

- When research occurs at a hospital, the pharmacy is responsible for managing and controlling devices.
- When research occurs outside a hospital, AEMPS must approve plans for managing and controlling devices.

Element I.7.C. The Organization has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.

The Spanish Agency of Medicines and Medical Devices (AEMPS) does not have the same requirements as the US FDA. When an investigational product is used for benefit of a specific participant, that is not considered a clinical study and does not require IRB/EC review.

Policies and procedures indicate:

- The administration of an investigational medicinal product to individual patients within the scope of standard medical practice and with the sole fundamental aim of achieving a therapeutic benefit for those patients shall not be considered a clinical trial with medicinal products. (Royal Decree 1015/2009, Royal Decree 1090/2015)

Standard I-8: The organization works with public, industry, and private Sponsors to apply the requirements of the Human Research Protection Program to all participants.

Element I.8.A. The organization has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.

Spain has specific provisions for research-related injuries that define the responsibilities of specific parties.

In clinical studies other than low-intervention clinical trials, the sponsor (Royal Decree 1090/2015, Article 9; Act 14/2007, Article 18):

- Must ensure that the trial subject is compensated for any damage suffered because of participating in the trial.
    - This compensation shall be independent of the financial capacity of the sponsor, investigator, and site.
- Must obtain insurance or a financial guarantee covering damage suffered as a result of participating in the trial, as well as any liability that might be incurred by the sponsor, principal investigator and members of the investigator team, including contracted clinical investigators, and the hospital or site where the clinical trial is conducted.
    - In the case of clinical trials included in the definition of "non-commercial clinical research", an application may be submitted without having contracted the insurance or financial guarantee. However, in the event of a favorable opinion from the IRB/EC, the decision on authorization of the trial shall be subject to the submission of this documentation to the IRB/EC within thirty calendar days and the study may not be started until the required insurance or financial guarantee is considered available.
- When a research participant could be injured as a result of participating in a low-intervention clinical trial, the sponsor does not need to obtain insurance or a financial guarantee if participation in the low-intervention clinical trial is covered by the insurance of individual or collective professional civil liability insurance or equivalent financial guarantee of the site where the clinical trial is conducted.
- When the sponsor and principal investigator are the same person and the clinical trial is conducted in a health center belonging to the public health administration, the administration may take the measures it

deems appropriate to facilitate the guarantee of the specific risks resulting from the trial in the terms set out in the above paragraphs, with the aim of promoting research.

Policies and procedures indicate that:

- It shall be presumed, unless proven otherwise, that any harm to the health of a trial subject during the trial and within one year from the end of treatment has occurred because of the trial.
    - Once the year has concluded, the trial subject is obliged to prove the connection between the trial and the harm caused.
    - All expenses derived from impairment in the health or physical status of the subject undergoing the clinical trial shall be considered liable for compensation, as well as any economic losses directly derived from such impairment, provided this is not inherent to the disease under study or due to the natural course of the disease as a result of the ineffectiveness of treatment.
    - The minimum amount that shall be guaranteed as civil liability shall be 250,000 Euros per subject undergoing the clinical trial, which may be received as a flat rate payment or as an income equivalent to the same capital. A maximum insured capital or maximum amount of the financial guarantee per clinical trial and per year of 2,500,000 Euros may be established.

Standard I-9: The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization the rights and welfare of research participants are protected.

When conducting or reviewing clinical studies, EU regulations and Spanish law supersede AAHRPP requirements for Standard I-9, when AAHRPP requirements conflict.

For research not covered by the EU CTR and/or EU MTR, policies and procedures describe how the organization meets AAHRPP requirements when reviewing for other organizations or relying upon other organizations for review of studies not covered by the EU CTR and/or EU MTR.

When participating in a clinical study, a clinical trial, or a low-intervention clinical trial, where another ethics committee in Spain (an external ethics committee) is designated by the CT-College as the reviewing ethics committee, policies and procedures must:

- Specify the use of the conflict-of-interest form required by EU application system (See Element I.6.B.).
- Describe the process and timelines for reporting to the external ethics committee as required by the CTR and MDR.
- When reporting is not required by a designated external ethics committee, policies must describe an internal process to require that researchers report to the researcher's own organization events, including unanticipated problems, participant complaints, protocol deviations, and other events, and a process for the organization to

review these reports and manage these reports to ensure participants are protected, even when reporting to the designated external ethics committee is not required. (See Elements II.2.G. and II.2.H.)

- Specify a contact person (by title or role) at the organization for researchers and research staff to obtain answers to questions, whether such contact information is provided by the external ethics committee.

When serving as the designated ethics committee by the Spanish Agency of Medicines and Medical Devices (AEMPS), policies must specify:

- Researchers must use the conflict-of-interest form required by the EU application. (EU and Spanish regulations do not provide for the ability of ethics committees to request disclosures of conflicts of interest by research staff.) (See Element I.6.B.)
- Reporting requirements for SUSARs and other events requiring reporting under the CTR and MDR.
- Who (role or title of person) is responsible for reporting suspensions and terminations of ethics committee approval via the EU European Portal and Database
- Who (role or title of person) responsible for updating the EU European Portal and Database of the ethics committee decisions.
- How the ethics committee IRB or EC will notify the researcher, and if applicable the researcher's organization, of its decisions.
- How researchers can contact the ethics committee (for example, via a website) by providing contact information for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the designated ethics committee.

For other research, not covered by the CTR or MDR, when reviewing for another organization or relying upon an external ethics committee, policies must address all requirements of Standard I-9.

Domain II: Institutional Review Board or Ethics Committee

Standard II-1: The structure and composition of the IRB or EC are appropriate to the amount and nature of the research reviewed and in accordance with requirements of applicable laws, regulations, codes, and guidance.

Element II.1.A. The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.

Organizations in Spain that rely on external IRBs/ECs should describe how they ensure the external IRB/EC meets regulatory requirements.

Spain defines an IRB/EC as follows (Royal Decree 1090/2015, Article 2):

- Ethics Committee for Investigation (CEI): An independent body with a multidisciplinary composition whose main purpose is to oversee the protection of the rights, safety and well-being of subjects participating in a biomedical investigation project and offer public assurance in this respect by giving an opinion on the corresponding documentation of the investigation project, taking into account the views of laypersons, in particular, patients or patient organizations.
- Ethics Committee for investigation with medicinal products (CEIm): Ethics Committee for Investigation which is also accredited in accordance with the terms of this Royal Decree to issue an opinion on a clinical study with medicinal products under EU CTR and on a clinical investigation with medical devices under EU MTR.

IRB/EC membership

Each IRB/EC has a minimum of ten members with varying backgrounds to promote complete and adequate review of research commonly conducted by the organization and ensure the independence of its decisions and the competence and experience of its members in the methodological, ethical and legal aspects of research, pharmacology, and clinical care practice in both hospital and community medicine (Royal Decree 1090/2015, Article 15):

- Each IRB/EC has at least one member whose primary concerns are in scientific areas.
- Each IRB/EC must include physicians, one of whom must be a clinical pharmacologist, a hospital or primary care pharmacist and a certified or graduate nurse.
- Each IRB/EC has at least one member whose primary concerns are in nonscientific areas.
- Each IRB must have at least two professionals outside the field of medicine, one of whom must be an attorney.
- Each IRB/EC must have at least one member with accredited training in bioethics.
- Each IRB/EC must include a layperson outside the field of biomedical investigation or clinical care, who shall represent the interests or perspective of research participants.
- Each ethics committee has at least one member who is not otherwise affiliated with the organization of the designated ethics committee and who is not part of the immediate family of a person who is affiliated with the organization.
- No IRB/EC has members who are all males or all females.
- No IRB/EC has members who represent a single profession.

Specific criteria for quorum do not appear to be described in the laws of Spain.

IRBs/ECs must have a stable professional technical secretary integrated into the organizational chart of the institution to which this person is assigned or from its supporting institutions is responsible to:

- Manage the activity of the CEIm.
- Function as the interlocutor on behalf of the CEIm as regards communication with all agents concerned, including the Spanish Agency of Medicines and Medical Devices.
- Ensure that the necessary on-site and non-site meetings are held so that the CEIm complies with its duties in the established time periods.
- Prepare, in collaboration with the members of the CEIm, any reports that are requested by the Spanish Agency of Medicines and Medical Devices or any other competent authority to maintain its accreditation as an CEIm.

The technical secretariat must have the following qualifications:

- Have a higher degree and knowledge of medicine, investigation methods, bioethics, pharmacology, and medicinal product regulation and biomedical investigation in general.
- Maintain specific facilities for the performance of their work under conditions that ensure confidentiality. They should have a suitable space for holding meetings and for the handling and filing of confidential documents.
- Computer equipment with sufficient capacity to manage all the information received and generated by the committee and connection to the information system of the country-specific database of clinical trials with medicinal products and the EU portal and EU database, when they are available.
- A specific annual financial budget, approved by the management of the institution, is to be used for training activities organized for members of the CEIm and, where appropriate, a budget allocated to allowances for attendance of its members or possible experts or guests.

Element II.1.D. The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.

Neither the IRB/EC as a whole nor any of its members may receive directly nor indirectly any remuneration from the study sponsor. (Royal Decree 1015/2009

Standard II-2: The IRB or EC systematically evaluates each research protocol or plan to ensure the protection of participants.

Element II.2.A. The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that

exemption determinations are not to be made by researchers or others who might have a conflict of interest regarding the studies.

Regulatory provisions for exemptions do not appear to be allowed in Spain.

Element II.2.C. The IRB or EC has and follows written policies and procedures to conduct limited review by the IRB or EC, if such procedures are used.

This type of review is applicable only to organizations that are required to follow US DHHS regulations; however, conducting limited IRB review is optional.

Unless provisions to exempt research exists in Spain, organizations in Spain would not be eligible to conduct limited IRB review, even when US DHHS regulations are followed.

Element II.2.G. The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate.

When serving as the designated ethics committee for a clinical study, the designated ethics committee follows CTR and Spanish law for reporting.

Organizations must report consistent with requirements in the ICH-GCP (E6)(R2) guideline, including:

- New information that might affect adversely the safety of the participants or the conduct of the clinical trial.
- Any changes that significantly affect the conduct of the clinical trial or increasing the risk to participants.

Element II.2.H. The IRB or EC has and follows written policies and procedures for suspending or terminating IRB or EC approval of research, if warranted, and for reporting these actions, when appropriate.

Organizations must report consistently with requirements in the ICH-GCP (E6)(R2) guideline:

- New information that might affect adversely the safety of the participants or the conduct of the clinical trial.
- Any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.

Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes, and guidance.

Element II.3.A. The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.

The reporting member state reviews the anticipated therapeutic and public health benefits and risks and inconveniences for the subject.

The reviewing IRB/EC must determine the investigation does not involve any disproportionate risks and inconvenience to the human being in relation to the potential benefits to be obtained. (Act 14/2007, Article 14)

For all other research other than clinical studies, policies must indicate the ethics committee conducts an analysis of the risks and potential benefits, as described in the *Evaluation Instrument.*

Element II.3.F. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.

When following the CTR, consent must be in writing and signed by the participant. (CTR Article 29)

Consent must be obtained in writing (Law 41/2002)

Information given to the participant, or the participant's legally authorized representative, must include:

- The nature, objectives, benefits, implications, risks and inconveniences of the clinical trial.
- The subject's rights and guarantees regarding his or her protection, including the right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification.
- The conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial.
- The possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical trial is discontinued.
- Information about the applicable damage compensation system in the event a participant is injured through participation in the clinical trial.
- The EU trial number and information about the availability of the clinical trial results.

Consent documents must be kept comprehensive, concise, clear, relevant, and understandable to a layperson.

Consent for other research must meet all AAHRPP requirements. In addition to the basic and additional Elements of Consent, the following consent disclosures must also be included under ICH-GCP(E6)(R2):

- The approval or favorable opinion by the IRB.
- The probability for random assignment to each treatment.
- The participant's responsibilities.
- The alternative procedures or treatment that might be available to the participant, and their important potential benefits and risks.
- When applicable, the reasonably foreseeable risks or inconveniences to an embryo, fetus, or nursing infant.

- The important potential benefits and risks of the alternative procedures or courses of treatment that may be available to the participant.
- When there is no intended clinical benefit to the participant, the participant should be made aware of this.
- A statement that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the participant's original medical records for verification of clinical trial procedures and data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally authorized representative is authorizing such access.
- A statement that if the results of the trial are published, the participant's identity will remain confidential.

Documentation of the consent process includes (ICH-GCP)(E6)(R2):

- Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the participant or by the participant's legally acceptable representative.
- Prior to a participant's participation in the trial, the written consent document should be signed and personally dated by the person who conducted the informed consent discussion.
- If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.
    - After the written consent document and any other written information to be provided to participants is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the consent document, the witness should sign and personally date the consent document.
    - By signing the consent document, the witness attests that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that consent was freely given by the participant or the participant's legally acceptable representative.
    - Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written consent document, and any other written information provided to the participants.
- When collection of biological samples is envisaged in the clinical trial, participants must be informed about the provisions with regard to the future use of the samples, including whether the samples may be destroyed after the study is completed, or be incorporated into a collection or an authorized biobank. Participants must be informed of

the biobank or the person responsible for collection, as well as the location where the samples shall be kept. (Royal Decree 1716/2011 of 18 November, Act 14/2007, Article 59)

- Consent documents must include information about how to access the Spanish Clinical Trials Registry, a database administered by the Spanish Agency of Medicines and Medical Devices; AEMPS), accessible on its website, publicly accessible and free of charge for any user, whose purpose is to serve as a source of information on clinical trials for the general public. (Royal Decree 1090/2015, Article 2)

Element II.3.G. The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.

Waivers or alterations of consent are not described in clinical trials of drugs and medical devices.

Observational studies with medications that involve interviewing the participating subject require informed consent, unless:

- The IRB/EC considers that observational research has an important social value.
- Its implementation would not be feasible or feasible without such a waiver, and
- The research involves minimal risks for the participants.

Standard II-4: The IRB or EC provides additional protection for individuals who are vulnerable to coercion or undue influence and participate in research.

Element II.4.A. The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.

A clinical trial on pregnant or breastfeeding women may be conducted only where the following conditions are met (EU CTR, Article 33; Act 14/2007, Article 19)

- The clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, fetus or child after birth, outweighing the risks and burdens involved.
- The investigation involves no more than minimum risk to the woman and, where appropriate, to the embryo, the fetus or the child.
- It is not possible to conduct research into people who are not pregnant.
- If such clinical trial has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, fetus or child after birth, it can be conducted only if:
    - A clinical trial of comparable effectiveness cannot be conducted on women who are not pregnant or breastfeeding.

    - The clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, fetuses or children; and
    - The clinical trial poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, fetus or child after birth.
- Where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child.
- No incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings related to participation in the clinical trial.

Research involving fetuses.

- The establishment of pre-embryos and human embryos exclusively for the purpose of experimentation is prohibited. (Act 14/2007, Article 28 and 33)
- Individuals engaged in the research will have no part in any decisions to terminate a pregnancy (Act 14/2007, Article 28)

Research involving live embryos and fetuses in the womb (Act 14/2007, Article 30)

- Research must provide a direct diagnostic or therapeutic benefit.

Clinical trials involving children may be conducted only where the following conditions are met (Royal Decree 1090/2015, Article 5; Act 14/2007, Article 4)

- An IRB/EC responsible for assessing a clinical trial on minors must have pediatric experts among their members or have obtained advice on the clinical, ethical and psychosocial issues in the field of pediatrics.
- The child will participate as far as possible and according to their age and capacity in decision-making throughout the research process.

Clinical trials on adults unable to consent / incapacitated participants may be conducted only where the following conditions are met (Royal Decree 1090/2015, Article 5, Act 14/2007, Article 20; ICH-GCP(E6)(R2))

- The IRB/EC has determined that the results of the research can produce real or direct benefits for the health of the participant.
- That comparable efficacy research cannot be performed on individuals able to provide consent.
- That participants are informed of their rights, unless the participant lacks decisional capacity.
- That the legal representatives of the person who is to participate in the investigation have given their written consent
- The protocol must be approved by an IRB/EC that has experts in the disease in question or has obtained advice from experts on the clinical, ethical and psychosocial problems in the field of the relevant disease and the patient population concerned.
- The IRB/EC must determine the investigator take steps to be reasonably sure that there are no previous instructions of the person expressed in

this regard before suffering a change in their capacity, which must be respected. This possibility and the procedure to be followed must be provided for in the trial documentation approved by the IRB/EC.

- If the research will not provide direct benefits to the health of the participants, then research may only be approved in the following conditions are met:
    - That the research has the object of contributing, through significant improvements in the understanding of the disease or condition of the individual, to a beneficial outcome for other people of the same age or with the same disease or condition, within a reasonable time.
    - That research involves a minimum risk and burden for the participating individual.
    - That the authorization of the investigation be brought to the attention of the Fiscal Ministry.
- Non-therapeutic clinical trials may be conducted in participants with the consent of a legally acceptable representative provided the following conditions are fulfilled (ICH-GCP(E6)(R2)):
    - The objectives of the clinical trial cannot be met by means of a trial in participants who can give consent personally.
    - The foreseeable risks for the participants are low.
    - The negative impact on the participant's wellbeing is minimized and low.
    - The clinical trial is not prohibited by law.
    - The opinion of the IRB/EC is expressly sought on the inclusion of such participants, and the written opinion covers this aspect.
    - Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

Research involving children may only occur when the following are met: (EU CTR, Article 32)

- The clinical trial is intended to investigate treatments for a medical condition that only occurs in minors, or the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods.
- The clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such nature that it can only be conducted on children.
- There are scientific grounds for expecting that participation in the clinical trial will produce:
    - A direct benefit to the minor outweighing the risks and burdens involved; or
    - Benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk, and will impose

minimal burden, on the minor concerned in comparison with the standard treatment of the minor's condition.

- The IRB/EC in charge of assessing Part II of a clinical trial on minors must have pediatric experts among their members or have obtained advice on the clinical, ethical and psychosocial issues in the field of pediatrics. (Royal Decree 1090/2015, Article 5)
- Parental permission and child assent are obtained (See Element II.4.B.)

Research involving prisoners.

Specific additional protections for prisoners involved in research in Spain do not appear to be described. However, as a vulnerable population, if organizations are allowed to conduct research involving prisoners, then policies and procedures should describe equivalent protections, such as:

- The clinical trial is intended to investigate treatments for a medical condition that occurs in prisoners.
- The clinical trial either relates directly to a medical condition from which prisoners suffer or is of such nature that it can only be conducted on prisoners.
- The research cannot be conducted in another population than amongst incarcerated people.
- There are scientific grounds for expecting that participation in the clinical trial will produce:
    - A direct benefit to the prisoner outweighing the risks and burdens involved; or
    - Benefit for the population represented by the prisoner concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the prisoner concerned in comparison with the standard treatment of the prisoner's condition.
- The IRB/EC in charge of assessing Part II of a clinical trial on prisoners must have a prisoner representative among its members or have obtained advice on the clinical, ethical and psychosocial issues in the field of prisons and incarceration.
- Consent is obtained.
- Appropriate permission from regulatory agencies is obtained, if applicable.

Element II.4.B. The IRB or EC has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question.

In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where the following conditions are met:

- The informed consent of their legally designated representative has been obtained.
- The incapacitated subjects have received consent disclosures in a way that is adequate in view of their capacity to understand it.

- The explicit wish of an incapacitated subject who can form an opinion and assess the consent disclosures to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator.
- No incentives or financial inducements are given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings related to the participation in the clinical trial.
- The clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods.
- The clinical trial relates directly to a medical condition from which the subject suffers.
- There are scientific grounds for expecting that participation in the clinical trial will produce:
    - A direct benefit to the incapacitated subject outweighing the risks and burdens involved; or
    - Some benefit for the population represented by the incapacitated subject concerned when the clinical trial relates directly to the life-threatening or debilitating medical condition from which the subject suffers and such trial will pose only minimal risk to, and will impose minimal burden on, the incapacitated subject concerned in comparison with the standard treatment of the incapacitated participant's condition.

Parental permission and assent for clinical trials – Clinical trials involving children may be conducted only where the following conditions are met (EU CTR, Article 32):

- The informed consent of their legally designated representative has been obtained.
- Children have received consent disclosures in a way that is adequate in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children.
- The explicit wish of a minor who can form an opinion and assess the consent disclosures to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator.
    - When the participant's condition allows, or in any case when the child is twelve years of age or older, the child participant must also give consent to participate in the trial. (Royal Decree 1090/2015, Article 3)
- No incentives or financial inducements are given to the subjects or their legally designated representatives, except for compensation for expenses and loss of earnings related to the participation in the clinical trial.

Element II.4.C. The IRB or EC has and follows written policies and procedures for making exceptions to consent requirements for planned

emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance.

Participants may be enrolled in research during emergency situations where the designated ethics committee determines and documents that (EU CTR, Article 35):

- Due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition.
- There are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition.
- It is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative.
- The investigator certifies that he or she is not aware of any objections to participating in the clinical trial previously expressed by the subject.
- The clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations
- The clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.
- Informed consent must be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements:
    - Regarding incapacitated participants and minors, the informed consent shall be sought by the investigator from his or her legally designated representative as soon as possible to the participant and to his or her legally designated representative.
    - Regarding other participants, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner.
- It is not possible to conduct comparable efficacy investigations in people who are not in that emergency situation. (Act 14/2007, Article 21)
- The participant or the participant’s legally authorized representative must be informed about the clinical trial as soon as possible and provides consent if the participant wishes to continue. (ICH-GCP(E6)(R2))

Domain III: Researcher and Research Staff

Standard III-1: In addition to following applicable laws and regulations, Researchers and Research Staff adhere to ethical principles and standards appropriate for their discipline. In designing and conducting research studies, Researchers and Research Staff have the protection of the rights and welfare of research participants as a primary concern.

Element III.1.C. Researchers employ sound study design in accordance with the standards of their discipline. Researchers design studies in a manner that minimizes risks to participants.

Policies and procedures specify that (ICH-GCP(E6)(R2)):

- During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial.
- The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding.
- A qualified physician (or dentist, when appropriate), who is a researcher or a co- researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions.
- Researchers inform participants when medical care is needed for other illnesses of which the researchers become aware.

Element III.1.E. Researchers and Research Staff recruit participants in a fair and equitable manner.

Policies and procedures specify that (ICH-GCP(E6)(R2)):

- The researcher informs the participant's primary physician about the participant's participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.
- Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the researcher makes a reasonable effort to ascertain the reason, while fully respecting the participant's rights.

Element III.1.F. Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.

Policies and procedures specify that (ICH-GCP(E6)(R2)):

- Researchers and research staff provide all the disclosures and follow the requirements pertaining to consent covered by ICH-GCP (E6).

Standard III-2: Researchers and Research Staff meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the organization's policies and procedures for protecting research participants; and the IRB's or EC's determinations.

Element III.2.A. Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the organization's policies and procedures regarding the protection of research participants.

Policies and procedures specify that (ICH-GCP(E6)(R2)):

- The researcher provides evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority.
- The researcher is familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator's brochure, in the product information, and in other information sources provided by the sponsor.
- A qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions (not applicable to independent IRBs).
- During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial (not applicable to independent IRBs).
- The researcher ensures the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.
- The researcher permits monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority.
- The researcher maintains the clinical trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements.
- Essential documents are retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.

Element III.2.B. Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions.

Policies and procedures specify that (ICH-GCP(E6)(R2)):

- The researcher must maintain a list of appropriately qualified people to whom they have delegated significant clinical trial-related duties.

Element III.2.D. Researchers and Research Staff follow reporting requirements in accordance with applicable laws, regulations, codes, and guidance; the organization's policies and procedures; and the IRB's or EC's requirements.

Policies and procedures specify that (ICH-GCP(E6)(R2)):

- The researcher must report all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., investigator's brochure) identifies as not needing immediate reporting. The researcher follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
- The researcher reports adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- For reported deaths, the researcher supplies the sponsor and the IRB/EC with any additional requested information (e.g., autopsy reports and terminal medical reports).
- The researcher provides written reports to the sponsor, the IRB, and, where applicable, the organization on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
- If the researcher terminates or suspends a clinical trial without prior agreement of the sponsor, the researcher informs the organization, sponsor, and the IRB.
- If the IRB/EC terminates or suspends approval of the clinical trial, the researcher promptly notifies the sponsor.
- Upon completion of the clinical trial, the researcher informs the organization; the IRB/EC with a summary of the trial's outcome; and the regulatory authority with any reports required.