**Logo institución**

|  |
| --- |
| **STUDY PROTOCOL** |
| TITLE: “**…..**”The study title reflects (if appropriate) the patient population, intervention (e.g. medicinal product or device), comparator (e.g. another intervention, placebo or usual care) and outcome. You might also consider incorporating the design type (e.g. a randomized controlled study, case-control study, or retrospective cohort study).You might also like to include a ‘lay’ (‘public’ or ‘simplified’) title easily understood by non-medical or interdisciplinary persons and/or an acronym. *e.g. “A randomized controlled study to evaluate the effect of tight glycaemic control in intensive care patients on survival”.* |
|  |
| **Version and date** | Version: xxx date: dd/mm/yyyy |
| **Protocol code or number** | *Optional* |
| **Short title**  | *Optional* |
| **Sponsor** |  |
| **CRO** | *If applicable* |
| **Funder**  | *If applicable* |
| **Study Investigator(s)** | Principal Investigator (A): Ms. xxxxxx1  Ph. Email: Principal Investigator (B): xxxxx2Co-Investigator (A): xxxxx1 Co-Investigator (B): xxxxx2Co-Investigator (C): xxxxx21. Institution, street, city, country, etc. 2: Institution, street, city, etc. |

**PROTOCOL APPROVAL**

Protocol code or number:

Title:

Investigator’s Statement and Signature

I have read and understand this protocol and concur with the study design. I agree to participate as a Principal Investigator and to follow the protocol as outlined.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Dr.

Principal Investigator Date

(Signature)

**Table of contents**

1. **Synopsis**

|  |  |
| --- | --- |
| **Title:** | <Full title> |
| **Study Description:** | *Provide a short description of the protocol, including a brief statement of the study hypothesis. This should be only a few sentences in length.*  |
| **Objectives:** | *Include the primary and secondary objectives.* |
|  | <Primary Objective:  |
|  | Secondary Objectives: >  |
| **Design/phase:** |  |
| **Endpoints:** | *Include the primary endpoint and secondary endpoints.* <Primary Endpoint:Secondary Endpoints: > |
| **Study Population:** | *Specify the sample size, gender, age, demographic group, general health status, and geographic location.* |
| **Description of Sites/Facilities Enrolling Participants:** | *Provide a brief description of planned facilities/participating sites enrolling participants. Indicate general number (quantity) of sites.* |
| **Description of Study Intervention:** | *Describe the study intervention. If the study intervention is a drug or biologic, include dose and route of administration. For devices, provide a description of each important component, ingredient, property and the principle of operation of the device.* |
| **Study Duration:** | *Estimated time (in months) from when the study opens to enrollment until completion of data analyses.* |
| **Participant Duration:** | *Time (e.g., in months) it will take for each individual participant to complete all participant visits.* |

***Flow diagram***

Prior to

Total N: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.

Enrollment

Randomize

Perform baseline assessments.

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Administer initial study intervention.

Visit 1

Time Point

Repeat study intervention (*if applicable*).

Visit 2

Time Point

Follow-up assessments of study endpoints and safety

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Visit 3

Time Point

Follow-up assessments of study endpoints and safety

<list specimens to be collected, examinations or imaging or laboratory assays to be performed, questionnaires to be completed OR refer to **Section 1.3, Schedule of Activities**>

Visit 4

Time Point

**Final Assessments**

<list analyses to be performed OR refer to **Section 1.3, Schedule of Activities**>

Visit X

Time Point

**Schedule of activities**

*The schedule of activities must capture the procedures that will be accomplished at each study visit, and all contact, with study participants e.g., telephone contacts. This includes any tests that are used for eligibility, participant randomization or stratification, or decisions on study intervention discontinuation. Only include procedures that contribute to participant eligibility and study objectives and endpoints.*

*e.g*

| **Procedures** | ScreeningDay … to … | Enrollment/BaselineVisit 1, Day … | Study Visit 2 Day … +/- … | Study Visit 3Day … +/- … | Study Visit 4Day …. +/- … | Study Visit 5Day … +/- … | Study Visit 6Day … +/- … | Study Visit 7Day ... +/- … | Study Visit 8Day …+/- … | Study Visit 9Day … +/- … | Study Visit 10Day … +/- … | Study Visit 11Day … +/- … | Study Visit 12Day … +/- … | Final Study Visit 13Day …. +/- … |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Informed consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demographics | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medical history | X |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomization |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Concomitant medication review | X | X---------------------------------------------------------------------------------------------X |  |
| Physical exam (including height and weight) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Vital signs |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Height |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Weight |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Performance status |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hematology  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| serum chemistry a |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pregnancy test |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adverse event review and evaluation | X | X---------------------------------------------------------------------------------------------X | X |
| Radiologic/Imaging assessment |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Other assessments (e.g., immunology assays, pharmacokinetic) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium. |

1. **Abbreviations**

|  |  |
| --- | --- |
| AE | Adverse Event |
| SAE | Serious Adverse Event |
| CRF | Case Report Form |
| eCRF | Electronic Case Report Forms |
| EC | Ethics Committee |
| PI | Principal Investigator |

1. **Protocol amendment history**

|  |  |  |  |
| --- | --- | --- | --- |
| **Version** | **Date** | **Description of Change**  | **Brief Rationale** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

1. **Background**
* *A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance.*
* *A summary of relevant clinical research and any history of human use or exposure to the study intervention, including use in other countries.*
* *Discuss the importance of the topic (public health and/or clinical importance and impact on individuals/community; incidence, prevalence, mortality and morbidity).*
* *Critically appraise the relevant literature and discuss the state of current knowledge on the topic (including deficiencies in knowledge or gaps that make the study worth doing).*
* *Indicate how the research question has emerged and fits logically with the above.*
* *Outline your approach to address the research question.*
* *Explain how your study will contribute to existing research and benefit other individuals or the wider community.*
1. **Aim(s) of Study**

*Your aim(s) should arise from your literature review and state what the study hopes to accomplish.*

1. **Hypothesis**

Your primary hypothesis is your statement of the hypothesised effect on the primary outcome measure. Hypotheses are generally stated in the null form (Ho) as they have their basis in inferential statistics. Rejecting the null hypothesis increases our confidence, with a given level of probability, that there is a relationship between the variables being studied. However, a classic scientific hypothesis includes both a null and alternative (Ha) hypothesis.

*e.g. H0: Asthma prevalence rates are not different among children from low and high socioeconomic groups in Istanbul.*

*HA: Asthma prevalence rates are different among children from low and high socioeconomic groups in Istanbul.*

1. **Objectives**

An objective is the purpose for performing the study in terms of the scientific question to be answered. Express each objective as a statement of purpose (e.g., to assess, to determine, to compare, to evaluate) and include the general purpose (e.g., efficacy, effectiveness, safety) and/or specific purpose (e.g., dose-response, superiority to placebo, effect of an intervention on disease incidence, disease severity, or health behaviour).

* 1. **Primary objectives**
	2. **Secondary objectives**
	3. **Exploratory objectives**
1. **Study Design**

A description of the type/design of trial to be conducted (e.g., randomized, placebo-controlled, double-blinded, parallel design, open-label, dose escalation, dose-ranging, adaptive, cluster randomized, group sequential, multi-regional, superiority or non-inferiority design, cross-sectional survey, prospective or retrospective cohort/case-control…).

A description of methods to be used to minimize bias.

Name of study intervention(s).

Note if interim analysis is planned.

1. **Rationale for study design**

Describe the rationale for the type and selection of control (e.g. placebo, active drug, dose-response, historical) and study design (e.g., non-inferiority as opposed to superiority). Discuss known or potential problems associated with the control group chosen in light of the specific disease and intervention(s) being studied.

1. **Study Setting/ Location**

The location of where the study will be conducted (e.g. oncology unit, Hospital del Mar). You need to mention whether the study is going to be a single-centre study or a multi-site study (i.e. conducted in more than one location).

1. **Study Population**

Defining the group in which the study will be carried out on provides the setting for which the research has relevance. This section also describes how one can be certain that the results from your sample population can be generalised to the target population of interest. This section should describe the target population, including:

* Population the subjects will be drawn from
* All aspects of subject selection
* The total number and number within any subgroups
1. **Eligibility Criteria**
	1. **Inclusion criteria**

Inclusion criteria are the ‘characteristics’ that clearly describe the study population that are required for a subject to be included in the study. The criteria may be based on factors such as age, gender, the type and stage of a disease, previous treatment history, and co-morbid medical conditions.

* 1. **Exclusion criteria**

Provide details of participants that will be considered ineligible to participate and justification for their exclusion. These criteria are not always clinical in nature, aiming principally to accommodate participants in a safe and ethical manner. Criteria may include circumstances that interfere with the participant’s ability to give informed consent (diminished understanding or comprehension), contraindications to the study treatment(s)/procedure(s), taking certain concomitant medication(s), or conditions that interfere with a patient's ability to comply with all treatment(s)/procedure(s).

* 1. **Subject early termination**

Subjects may withdraw from the study at any time with no obligation to provide a reason or the PI may terminate a subject from the study for safety or efficacy reasons.

The reasons for withdrawing from the study will be as follows:

* Screening failure: Any patient who, once informed and has consented to participate in the study, does not meet the inclusion and/or exclusion criteria.
* Withdrawal of consent: Any patient who, for any reason, withdraws her/his consent
* Adverse Events: ………
* Serious Adverse Events: ………
* Lost to follow-up: …….
* Study termination: ……
1. **Study treatment**
	1. **Investigational products**

|  |  |  |
| --- | --- | --- |
|  | **Drug 1** | **Drug 2** |
| Dose daily |  |  |
| Trade name |  |  |
| Formulation  |  |  |
| Route of administration |  |  |
| Dosage schedule |  |  |

* 1. **Randomization**

Include the method (including any software) used to generate the random allocation sequence. Describe type of randomisation performed, ratio of assignment to groups*,* block size permutation and stratification if applicable. Explain the methods used to conceal group allocation until assignment. Also, include information on who will generate the allocation sequence and who will assign participants into their groups.

This section should also discuss if participants, the investigator, and those assessing/analyzing the outcome(s) will be blind (or masked) to group assignment or if the study will be an open-label study (investigators and subjects know their assigned group).

* 1. **Labeling**
	2. **Treatment administered**
	3. **Concomitant medication**
1. **Study Outcomes**
	1. **Primary Outcome(s)**

The primary outcome should be the most important and clinically relevant outcome (e.g. clinical, psychological, economic, or other) of the study. This isthe measure used to answer your study aim. However, it is also the outcome used to calculate study sample size and power and test the primary research hypothesis.

Primary outcome measures may be measured in various ways such as: binary (e.g. caesarean/no caesarean, blood loss ≥500mL/blood loss <500mL); continuous (e.g. weight - kg, blood loss - mL); ordinal (e.g. pain - mild, moderate, severe); time to event (e.g. survival), and counts (e.g. number of infections, number of events occurring).

* 1. **Secondary Outcome(s)**

Secondary outcome(s) are measures of additional or less important research interest. They may include additional clinical, psychological, economic, or safety outcomes (e.g. treatment related side effects/adverse events). However, as these endpoints are not used to calculate study power and sample size it is often not possible to draw robust conclusions from the results.

1. **Study Procedures**
	1. **Recruitment**

This section should describe which potential participants will be identified/selected for recruitment (e.g. via outpatient clinic, medical records search), how they will be approached/invited to participate and how consent will be obtained. You may need to justify the feasibility of recruiting the required number of subjects and estimate the proportion that you would expect will agree to participate. Finally, the period of time expected to recruit the required number of participants should be stated here.

* 1. **Study procedure**

In this section you need to clearly and comprehensively describe exactly what will happen to participants once they are enrolled in your study. Depending on the study it might include how potential participants will be approached, when they will be randomised, the frequency and duration of visits or whether they are expected to self-complete a daily diary at home, the duration of the study or follow-up, and any measurements taken at each visit (e.g. questionnaires, physical measurements, biological samples).

You should include precise details of the treatment(s)/intervention(s) intended for each group/participant. You should also provide details of any follow-up schedule (i.e. time between visits) and consider how you will monitor participants’ adherence with the treatment schedule. You might also describe under which circumstances participants may be withdrawn and how this will occur. A schematic diagram or flow chart may be useful for this section.

For drugs and devices that are commercially available, the protocol must state their proprietary names, manufacturer, chemical composition, dose, duration and frequency of administration.

* 1. **Measurement tools used**

It is essential to state how the data will be collected to assess the primary and secondary outcome(s) of the study (e.g. patient questionnaire, medical charts, routinely collected hospital/research database, biological specimens). Describe at what point(s) of the study data collection will occur. You should make statements that justify the validity of the study measure/instrument. If not, you will have to verify how you will ensure the validity and quality of data being collected. Also, mention here if you are going to have one or more assessors to collect data, their level of training/experience (or how they will be trained), and if you are planning to assess inter-rater reliability (if applicable).

* 1. **End of the study**

Definition of the end of the study. For example: Last Visit of Last Patient (LVLP).

1. **Evaluation of Efficacy**
2. **Evaluation of Safety**

The safety of research participants is foremost. You will need to provide adequate information on how the safety of research participants will be ensured. This can include procedures for recording and reporting adverse events (and serious adverse events) and their follow-up (mandatory requirement for studies involving intervention or treatments). Remember that even administering a research questionnaire may have adverse psychological effects on susceptible individuals.

1. **Statistical Considerations and Data Analysis**
	1. **Sample size and statistical power**

A sample size or power calculation should be performed. This calculation is used to estimate the number of subjects required to answer your primary study hypothesis with an accepted power. Conversely, it also allows you to estimate what power can be achieved with a limited number of participants. This number is calculated by specifying the magnitude of the effects that are expected (i.e. informed and clinically significant), variability of the measurements and the acceptable degree of type I and II errors. You need to specify the assumptions made for the calculation. It is recommended that you consult with a statistician for this section. Also keep in mind the estimated recruitment rate and whether you need to adjust for anticipated non-responders and losses to follow up.

* 1. **Statistical Analysis**

The statistical methods used for the study objectives/hypotheses (e.g. t-test, chi-squared, multivariate modeling) must be sufficiently detailed. If conducting a randomized controlled study, you should state whether methods will include an “intention to treat” (ITT) analysis, per protocol analysis, or both. An ITT analysis is preferred as it compares all subjects in the groups to which they were originally randomly assigned (despite withdrawal, treatment failure or cross-over).

* 1. **Limitations**

Explain the limitations of the study if it is applicable.

1. **Ethical Considerations**

The study will be conducted in full conformance with principles of the Declaration of Helsinki (Fortaleza, Brasil, 2013), Good Clinical Practice (GCP) and within the laws and regulations of the country in which the research is conducted.

* 1. **Study insurance**

*For low interventional trials:*

*The sponsor has a local insurance for the trial participants including the trial patients for the required duration of time, in accordance with the RD1090/2015.*

*This clinical trial fulfils all the conditions to be considered a "low intervention clinical trial”: (a) the investigational medicinal products, excluding placebos, are authorised; (b) according to the protocol of the clinical trial, (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) 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 (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.*

* 1. **Informed consent process**

Information on how informed consent is to be obtained should be included. This ensures that if participants can read and understand the information they need to make an informed decision about their voluntary participation. This can include allowances for special population groups (e.g. children, Aboriginal and Torres Strait Islander) where applicable.

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol <insert list>.

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Consent forms will be approved by the local ethics committee and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant’s comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

* 1. **Confidentiality and privacy**

You will also need to adequately detail methods of data extraction (non-identifiable, de-identified or re-identifiable), and data management, storage and security storage (of paper hardcopies and/or electronic files).

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions, according to the Spanish law (Organic Law 3/2018, of December 5, on Data Protection and Guarantee of Digital Rights). This confidentiality is extended to cover …. (e.g. testing of biological samples and genetic tests in addition to the clinical information relating to participants). Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Representatives of the sponsor, ethics committee or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the <specify name of Data Coordinating Center>. This will not include the participant’s contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by <specify name of Data Coordinating Center> research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the <specify name of Data Coordinating Center>.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>. The data system includes protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

* 1. **Future use of stored specimens and data (if applicable)**

Data collected for this study will be analyzed and stored at the <specify name of Data Coordinating Center>. After the study is completed, the de-identified, archived data will be transmitted to and stored at the <specify name of Data Repository>, for use by other researchers including those outside of the study. Permission to transmit data to the <specify name of Data Repository> will be included in the informed consent.

With the participant’s approval and as approved by local ethics committee, de-identified biological samples will be <removed / stored at the specify name of Biosample Repository>. These samples could be used to research the causes of <specify condition(s)>, its complications and other conditions for which individuals with <specify condition(s)> are at increased risk, and to improve treatment. The <specify name of Repository> will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

1. **Source Documents**
2. **Publication Policy**
3. **Outcomes and Significance**

It may be of value to reiterate the potential benefits of answering the research question and conducting the project. This section restates the justification for the study in terms of the anticipated results. It may be important to specify the implications of the potential results and how the results of this study may inform future research.

1. **References**
2. **Appendix**
	1. **Definition of AE and SAE**

**Acontecimientos adversos**

**Definiciones**

El Real Decreto 1090/2015 de 4 de diciembre de 2015 (BOE núm. 307, de 24 de diciembre de 2015) núm. 33, de 7 de febrero de 2004), en el artículo 2 define como acontecimiento adverso (AA) a cualquier incidente perjudicial para la salud que sobreviene a un sujeto de ensayo al que se ha administrado un medicamento, aunque no tenga necesariamente relación causal con el mismo.

Define como reacción adversa toda reacción nociva y no intencionada a un medicamento en investigación, independientemente de la dosis administrada.

Un acontecimiento adverso o reacción adversa puede ser:

* Grave es aquel que, a cualquier dosis, produzca la muerte, amenace la vida del sujeto, haga necesaria la hospitalización o la prolongación de ésta, produzca invalidez o incapacidad permanente o importante, o dé lugar a una anomalía o malformación congénita. A efectos de su notificación, se tratarán también como graves aquellas sospechas de acontecimientos adversos o reacción adversa que se consideren importantes desde el punto de vista médico, aunque no cumplan los criterios anteriores.
* Inesperado cuando la naturaleza o gravedad no se corresponde con la información referente al producto (por ejemplo, el manual del investigador en el caso de un medicamento en investigación no autorizado para su comercialización, o la ficha técnica del producto en el caso de un medicamento autorizado)

**Clasificación de los acontecimientos adversos**.

En este ensayo clínico, ante la aparición de un AA, el investigador deberá caracterizar su intensidad y la posible relación de causalidad con el fármaco en estudio.

Intensidad:

* **Leve**: acontecimientos adversos banales, de poca importancia y corta duración que no afectan sustancialmente la vida del paciente.
* **Moderada**: acontecimientos adversos que causan la suficiente incomodidad para interferir con la vida normal del paciente.
* **Severa**: acontecimientos adversos que suponen una incapacidad para trabajar o realizar la actividad habitual del paciente

Causalidad:

La relación de causalidad de un acontecimiento adverso con la medicación se establecerá según las definiciones de la OMS (Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994; 10:93-102) a las que se añade la categoría de “no relacionada”.

* Segura (Muy Probable): acontecimiento clínico (o evento clínico), incluídas anomalías en las pruebas de laboratorio, que se produce con una secuencia temporal plausible respecto a la administración del fármaco, y que no puede ser explicado por la enfermedad concurrente o por otros fármacos o sustancias químicas. La respuesta a la retirada del fármaco debe ser clínicamente plausible. El acontecimiento debe ser  definitivo farmacológica o fenomenológicamente, utilizándose  si es necesario el procedimiento de reexposición que debe ser positivo.
* Probable: un acontecimiento clínico, incluidas anomalías en las pruebas de laboratorio, que se produce con una secuencia  temporal razonable a la administración del fármaco, que es poco probable que pueda atribuirse a la enfermedad intercurrente o a otros fármacos o sustancias químicas, y que después de ser retirado el fármaco sigue una secuencia clínica razonable. No se requiere reexposición para completar esta definición.
* Posible: un acontecimiento clínico, incluidas anomalías en las pruebas de laboratorio, que se produce con una secuencia temporal de administración del fármaco razonable, pero que también podría explicarse por la enfermedad concurrente u otros fármacos o sustancias químicas. La información sobre la retirada puede no existir o ser confusa.
* Improbable: un acontecimiento clínico, incluidas anomalías en las pruebas de laboratorio, con una relación temporal respecto a la administración del fármaco que hace improbable la relación de causalidad, y en el que otros fármacos, sustancias químicas o enfermedad intercurrente proporcionan explicaciones plausibles.
* Condicional/Inclasificado: un acontecimiento clínico, incluidas anomalías en las pruebas de laboratorio, comunicado como una reacción adversa, del que o bien se necesitan más datos para una apropiada valoración o estos datos se encuentran pendientes de examen.
* No valorable/Inclasificable: una comunicación que sugiere un efecto adverso que no puede ser juzgado porque la información es insuficiente o contradictoria, y que no puede ser complementada o verificada.
* No relacionado: un acontecimiento clínico, incluidas anomalías en las pruebas de laboratorio, sin una relación temporal respecto a la administración del fármaco y en el que otros factores proporcionan explicaciones plausibles.

**Como notificar un acontecimiento adverso**

La vigilancia de la seguridad de los medicamentos en investigación debe realizarse de acuerdo con lo establecido en el Real Decreto 1090/2015 y teniendo en cuenta la guía detallada sobre la recogida, verificación y presentación de las notificaciones de reacciones adversas ocurridas en ensayos clínicos con medicamentos de uso humano (consultar www.agemed.es en el vínculo “Investigación Clínica”, y concretamente en “Ensayos clínicos con medicamentos de uso humano”).

**Notificación expeditiva de reacciones adversas graves e inesperadas en un EC**

La vigilancia de la seguridad de los medicamentos en investigación debe realizarse de acuerdo con lo establecido en el Real Decreto 1090/2015 y teniendo en cuenta la guía detallada sobre la recogida, verificación y presentación de las notificaciones de reacciones adversas ocurridas en ensayos clínicos con medicamentos de uso humano

<http://ec.europa.eu/health/files/eudralex/vol10/2011_c172_01/2011_c172_01_en.pdf>.

El promotor deberá notificar a la Agencia Española de Medicamentos y Productos Sanitarios todas las sospechas de reacciones adversas graves y, a la vez, inesperadas, asociadas a los medicamentos en investigación que hayan ocurrido en el ensayo clínico. En todos los casos, dicha notificación se realizará a través de la base de datos europea Eudravigilance\_CTM.

El plazo máximo de notificación es de 15 días naturales desde que el promotor tiene conocimiento de las sospechas de RAGI y de 7 días, si la RAGI ha ocasionado la muerte o puesto en peligro la vida del sujeto. Cuando sea preciso para garantizar la notificación rápida, el promotor podrá realizar una notificación inicial incompleta que deberá ser completada en lo posible en los ocho días siguientes.

**Notificación expeditiva de reacciones adversas graves e inesperadas en un EC a los CEIm y CCAA**

La Agencia Española de Medicamentos y Productos Sanitarios proveerá un sistema por el que las sospechas de reacciones adversas, que sean a la vez graves e inesperadas, asociadas al medicamento en investigación y que hayan ocurrido en pacientes incluidos en el ensayo clínico en España estén disponibles para los órganos competentes de las comunidades autónomas en tiempo real a través del sistema de información de ensayos clínicos.

Mientras no se disponga de un sistema de intercambio de información electrónico válido para todas las comunidades autónomas, se deberá notificar al órgano competente de cada una de las Comunidades Autónomas donde se realiza el ensayo las sospechas de RAGI ocurridas en los centros sanitarios de su Comunidad. Para ello se utilizará para ello el formulario de notificación que consta como anexo III.

Para el caso de Cataluña:

Aspectos generales y notificación de Reacciones Adversas e informes de seguridad

Unidad: Subdirección General de Farmacia y Productos Sanitarios. Dirección General de Recursos Sanitarios del Departament de Sanitat i Seguretat Social.

C/ Gran Vía 587 3ª planta. 08007 BARCELONA

Fax: 93482 45 27

Personas de contacto: Sr. Salvador Cassany Pou. Telf: 934824185; scassany@ics.scs.es; <http://www.gencat.net/sanitat>

**Otros acontecimientos adversos no RAGI**

La información sobre acontecimientos adversos graves esperados, los no graves y aquellos que se consideren no relacionados con los tratamientos en estudio será incluida de forma tabulada en el informe anual o final del ensayo clínico.

**Registro de acontecimientos adversos**

Los posibles acontecimientos adversos (efectos indeseables) y efectos farmacológicos se registrarán por parte de los investigadores cuando se manifiesten de forma espontánea por los sujetos o sean evidentes al investigador. La información que se obtenga se anotará en el apartado correspondiente de la hoja de registro de datos de cada sesión, que incluirá el tipo de efecto indeseable, su severidad, la causalidad, duración, tiempo de aparición, resultado final y el tipo de medidas correctoras si se emplean. Si es preciso se cumplimentará el formulario específico de notificación antes mencionado. Los posibles efectos sobre parámetros analíticos de sangre y orina se estudiarán mediante analítica en sangre y orina realizados en los tiempos que se especifiquen. Si se observan efectos indeseables (clínicos o analíticos), los sujetos permanecerán bajo control médico durante su evolución. Si los efectos indeseables observados son clínicamente significativos, se excluirá el voluntario afectado del ensayo y se valorará la posible suspensión del estudio.

El investigador está obligado a notificar inmediatamente al promotor de todos los acontecimientos adversos graves o inesperados que se produzcan, por vía telefónica o telefax dentro de las 24 horas posteriores a tener conocimiento del mismo, salvo cuando se trate de los señalados en el protocolo como acontecimientos que no requieran comunicación inmediata. La comunicación inicial irá seguida de comunicaciones escritas pormenorizadas.

El Promotor comunicará a la AEMPS el RAGI en el plazo máximo de 7 días si se trata de un AA mortal o que entrañe riesgo vital (aquellos que de no haber mediado una intervención terapéutica inmediata hubiera supuesto la muerte del paciente). Si no se dispusiera de toda la información, ésta podrá completarse en el plazo de 8 días adicionales. Los demás AA graves e inesperados se comunicarán en el plazo máximo de 15 días.

Es responsabilidad del Promotor la notificación de AA graves e inesperados al Comité Ético de Investigación con medicamentos, a la Agencia Española del Medicamento y Productos Sanitarios y al Centro de Farmacovigilancia de Cataluña.

En las comunicaciones iniciales y en las de seguimiento se identificará a los sujetos del ensayo mediante un número de código específico para cada uno de ellos.

Los acontecimientos adversos y/o los resultados de laboratorio anómalos calificados en el protocolo como determinantes para las evaluaciones de seguridad se comunicaran al promotor con arreglo a los requisitos de comunicación y dentro de los periodos especificados en el protocolo.

* 1. **Formulario de notificación de reacción adversa grave e inesperada ocurrida en España**



**INSTRUCCIONES GENERALES**

1. Este formulario se utilizará solamente para comunicar las sospechas de reacciones adversas (RA) graves e inesperadas que ocurran con medicamentos en investigación.

2. Las sospechas de RA mortales o que entrañen riesgo vital (aquellas que de no haber mediado una intervención terapéutica inmediata hubieran supuesto la muerte del paciente) se comunicarán en el plazo máximo de 7 días naturales; si no se dispusiera de toda la información, ésta podrá completarse en el plazo adicional de 8 días. Las demás sospechas de RA graves e inesperadas se comunicarán en el plazo máximo de 15 días.

3. Cuando el espacio disponible sea insuficiente, se añadirá una hoja de información adicional, correctamente identificada con el nombre del promotor y el número asignado a la notificación. En dicha información podrá hacerse constar la evaluación de la causalidad realizada por el técnico que informa.

**INSTRUCCIONES ESPECÍFICAS**

Ø. El código de protocolo es el asignado por el promotor para identificar el ensayo. El número de notificación del promotor es el que éste utiliza para su archivo. Cuando se trate de información de seguimiento se utilizará el mismo número o bien, si se modifica, se indicará el número de la notificación inicial. Se dejará sin rellenar el espacio “Nº de notificación” que aparece sombreado.

2. La edad se pondrá en años, meses, semanas o días según convenga, pero siempre indicándolo. Si no se conoce con precisión la edad debe referirse, al menos, el grupo de edad al que pertenece (p. ej.: lactante, niño, adolescente, adulto, anciano).

7. Se describirá la RA en forma completa, indicando la fecha de finalización de la misma e incluyendo los resultados de las exploraciones complementarias o pruebas de laboratorio que se consideren de interés. A esta notificación podrán acompañarse cuantos informes se estimen convenientes para la adecuada interpretación del cuadro clínico sospechoso de ser una reacción adversa.

8-13. Las categorías no son mutuamente excluyentes. La asistencia en un Servicio de Urgencias de un Hospital inferior a 24 horas, no se considerará hospitalización.

14. Los medicamentos en investigación se identificarán a ser posible por su nombre genérico (DOE o DCI), indicando cuando esté disponible el nombre comercial, o en su defecto, por el nombre propuesto o código de laboratorio para el producto.

15. En caso de que la administración no sea diaria se intentará describirla con alguna de las siguientes posibilidades: cíclica, semanal, mensual, anual o número de veces que se ha utilizado (poniendo en este caso la dosis de cada toma, no la total).

17. Se hará constar el proceso patológico del paciente al que va destinado el producto en investigación, o bien “voluntario sano” en caso de tratarse de tal.

19. Se hará constar la duración del tratamiento hasta el inicio de la reacción adversa.

22. Se indicará explícitamente si no se han tomado fármacos concomitantes. En el caso de considerar sospechoso alguno o algunos de los fármacos concomitantes se marcarán con un asterisco (p.ej.: \* AMOXICILINA). Se excluirán los medicamentos utilizados para tratar la reacción adversa.