**Logo institución**

|  |
| --- |
| **PROTOCOL** |
| TITLE: “**…..**” |
|  |
| **Version and date** | Version: xxx date: dd/mm/yyyy |
| **Protocol code or number** | *Optional* |
| **Short title**  | *Optional* |
| **Sponsor** |  |
| **CRO** | *If applicable* |
| **Funder**  | *If applicable* |
| **List of study Investigator and roles** | Principal Investigators:Name:Service:Site:Email:Telephone:Co-Investigators:Name:Service:Site:Email:Telephone: |

**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***

**Schedule of activities**

*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 |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

1. **Abbreviations**

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

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, observational, 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:

…..

p.e.

* 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 / study interventions (if applicable)**
	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 procedures**

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 (if applicable)**
2. **Evaluation of Safety (if applicable)**

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 (if applicable)**

*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 (or justify its exemption)**

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**