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| Public | *🞏 All 🗹 Investigators 🞏 Study Nurse 🞏 Study coordinator 🞏 Paramedics 🞏 Admin Staff*  |
| Document revision history / Changes-Revision Comment |  |

**This protocol redaction plan is intended to be used irrespective of the type of biomedical research. It must be adapted to each project. Some chapters are not systematically informed.
It aims to be usable for scientific and regulatory purposes.**

# Title Page

The title page should contain the following information:

* Protocol title (Clear, precise, short but informative enough)
* Clinical Development phase in case of drug
* Acronym
* Protocol identification (code or number)
* Name of test drug/investigational product/device.
* If not apparent from the title, a brief (one to two sentences) description giving design (parallel, cross-over, blinding, randomized) comparison (placebo, active, dose/response), duration, dose, and patient population
* Name and affiliation of principal investigator (address and phone number)
* Name and affiliation of coordinating investigator(s) (address and phone number)
* Name of the Sponsor including the name of Responsible medical head and address and phone/fax numbers
* EudraCT Number
* Version and date of protocole

Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor or Institution (principal Investigator, sub investigators).

Statement indicating whether the study will be performed in compliance with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (GCP) and local Ethic Committee and appropriate guidelines.

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Confidential
Cannot be used, disclosed, published without the consent of the Hôpital Erasme.**

# Signature page

**Sponsor Representative**

 Name Signature Date

**INVESTIGATOR (S)**

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated by CUB – Hôpital Erasme, with or without cause.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I will ensure that the requirements relating to Ethics Committee review and approval are met. I will provide CUB – Hôpital Erasme with any material which is provided to the EC for Ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the EC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without EC approval, except where necessary to ensure the safety of study participants.

 Name Signature Date

 Name Signature Date

# Protocol synopsis (2-3 pages)

|  |
| --- |
| Name of Sponsor/Company: |
| Name of Finished Product/device: |
| Name of Active Ingredient/device: |
| Title of Study |
| Indication |
| Study centre(s)  |
| Publication (reference) |
| Studied period (years): (date of first enrolment) (date of last completed)  | Clinical Phase:  |
| Objectives: - Primary - Secondary |
| Hypotheses |
| Study Design (Treatment Schema) |
| Number of patients (planned and analysed) |
| Endpoints : - Primary- Secondary |
| Diagnosis |
| Main criteria for inclusion |
| IP dosage and mode of administration (in case of drug):  |
| Procedures : Schedule of assessments (e.g. in Appendix) |
| Duration of treatment :  |
| Statistical Considerations |

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* Page number or other locating information of each section, including summary tables, figures, and graphs
* A list and the locations of appendices, tabulations, and any case report forms provided

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# Study Glossary

* List of abbreviations and definitions

# Ethics

* *This protocol, any protocol amendments, informed consent form and other relevant documents (eg. recruitment advertisements) will be submitted to the Erasme Hospital Ethics Committee for formal approval to conduct the study. The decision of the EC concerning the conduct of the study will be made in writing to the investigator. All correspondence with the IRB/IEC should be retained in the Investigator File:*
* *The study will be conducted in accordance with legal and regulatory requirements (Belgian law of 7 May 2004, Patient rights (08/2002), Private life (RD 2001), HBM (Human Body Material, law of 19 December 2008)), as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the last version of Declaration of Helsinki (World Medical Association).*
* *All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC. The formal consent of a subject, using the EC-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. The written informed consent document should be prepared in the language of the potential patient population.*
* Include procedures for maintaining subject confidentiality, any special data security requirements, and record retention per the sponsor’s requirements

# Objectives

Goals are broad statements of what the proposal hopes to accomplish. They create a setting for the proposal. Specific objectives are statements of the research question(s). Objectives should be simple (not complex), specific (not vague), and stated in advance (not after the research is done). After statement of the primary objective, secondary objectives may be mentioned.

## Primary

## Secondary

## Endpoints

# Background Information and Scientific Rationale

## Medical Background

Literature Revue: (references listed)

* The name and description of the study intervention/investigational products(s)
* Scientific explanation to define the issue :Discussion of important literature and data that are relevant to the trial and that provide background for the trial
* Justification of the study considering the current knowledge: A summary of findings from nonclinical in vitro or in vivo studies that have potential clinical significance, and a summary from relevant clinical trials
* Benefits expected for the research : Importance of the study and any relevant treatment issues or controversies
* Perspectives for the scientific community, the hospital, the public health.

## Drug Profile

If drug: substance, toxicology, pharmacokinetics, clinical studies.

If device: characteristics.

## Rationale

* Description of the route of administration and justification, dosage, dosing regimen, intervention periods, and selection of study population
* Statement of the hypothesis
* Discussion of known risks and benefits, if any, to human subjects

# Investigational plan

## Design

Definition of the characteristics of the biomedical research by standard terms

* Physio-(patho)logical experimentation, genetic, epidemiological, genetics, therapy,…
* Monocenter or multicenter (national or international) ; number of centers
* Clinical Phase
* With or without direct individual benefit
* nature of control(s) (e.g., placebo, no treatment, active drug, dose-response)
* Method of assignment to treatment (randomization, stratification)
* Number of study groups/arms
* Level and method of blinding/masking (e.g., open, double-blind, single-blind, blinded evaluators, and unblinded patients and/or investigators)
* Prospective, retrospective
* Study configuration : parallel groups or cross-over
* Approximate time to complete study enrollment
* Expected duration of subject participation
* Description of the sequence and duration of all trial periods, including follow-up
* Methods for collecting data for assessment of study objectives
* Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)
* Interim analysis plans

## Description of population

* Patient population studied
* Number of patients planned

## S*trategies for participant recruitment*

Consider where subjects will be recruited and how (consultation, advertising,…)

## Participants eligibility

Characteristics of the subjects to be included: age, sex, weight, size, race, medical history, biological parameters, definition of the pathology and the enumeration of its characteristics.

### Inclusion criteria

 Provide a statement that subjects must meet all of the inclusion criteria in order to be eligible to participate in the study and then list each criterion.

### Exclusion criteria

 Provide a statement that all subjects meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

### Withdrawal

Provide a list of reasons for which subjects may be discontinued from the study. Also note that subjects may withdraw voluntarily from participation in the study at any time. Describe the efforts to follow subjects who withdraw from the study.

## Treatments

### Treatments Administered

The precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, should be described.

 Route and mode of administration, dose, and dosage schedule.

### Identity of Investigational Products(s)

 Brief description of the test drug(s)/investigational product(s) (formulation, strength, storage, dose)

### Method of Assigning Participant to Treatment Groups

The specific methods used to assign patients to treatment groups, to screen and randomize eligible patient, perform subsequent assignment, manage initial/resupply ordering of drug supplies and handle emergency unblinding (e.g. IVRS, IWRS …) should be described.

### Selection of Doses in the Study

The doses or dose ranges used in the study should be given for all treatments and the basis for choosing them described (e.g., prior experience in humans, animal data).

### Selection and Timing of Dose for Each Patient

Assignment of medication numbers to eligible patients should be described (e.g. IVRS, IWRS …).

Time of day, interval of dosing and the relation of dosing to meals should be described and, if timing was not specified, this should be noted.

### Blinding

Procedure for breaking the blinding or rationale for no blinding should be explained.

### Prior and concomitant therapy

* Medication allowed before and during the trial
* Drug-drug interactions and effect on trial endpoints

### Treatment Compliance

Description of measures taken to ensure and document treatment compliance (e.g., drug accountability, diary cards, blood, urine or other body fluid drug level measurements, or medication event monitoring).

## Study Procedures

Refer to the Schedule of Assessments (Flowchart in Appendix)

The schedule must include clinic visits (screening, study period, follow-up visits), all contacts (e.g., telephone contacts) andall study procedures to be done during the protocol.

The protocol should specify the time that each phase of the project is likely to take, along with a detailed month by month timeline for each activity to be undertaken.

## Efficacy and Safety Variables

### Efficacy and Safety Measurements Assessed and Flow Chart

Schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration), methods for measurements and persons responsible, specific instructions, definitions used to characterize outcome, laboratory techniques.

Means of obtaining AE data.

AE rating (seriousness, severity).

### Appropriateness of Measurements

If any of the efficacy or safety assessments was not standard, its reliability, accuracy, and relevance should be documented.

### Primary Efficacy Variable(s)

The primary measurements and endpoints used to determine efficacy should be clearly specified.

### Drug Concentration Measurements

* Drug concentrations to be measured
* Sample collection times
* Periods in relation to the timing of drug administration
* Relation of drug administration and sampling to ingestion of food, posture, and the possible effects of concomitant medication/alcohol/ caffeine/nicotine
* Biological sample measured, handling of samples (storage, labeling …) and method of measurement used (referring to published and/or internal assay validation documentation for methodological details).
* Other (e.g. pharmacodynamics, pharmacogenomics, …)
* Samples shipment: frequency, address andcontact information for laboratory personnel (Include days and times shipments are allowed, any labeling requirements for specimen shipping and any special instructions such as dry ice or wet ice or the completion of a specimen-tracking)

## Safety Reporting

### Definitions

* Adverse Event: *See ICH E6 GCP, Section 1.2.*

*An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.*

* Serious Adverse Event: *See ICH E6 GCP, Section 1.50.*

*A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:*

* *Results in death;*
* *Is life-threatening (immediate risk of death);*
* *Requires inpatient hospitalization or prolongation of existing hospitalization;*
* *Results in persistent or significant disability/incapacity;*
* *Results in congenital anomaly/birth defect.*

### Assessing, Recording, and Analyzing Safety Parameters

* Based on the risk profile of the study product. Include a review of relevant literature, which should be referenced.
* Describe how the safety of research participants will be ensured
* Consider whether all non-serious AE’s need to be recorded taking into account the safety profile of the IMP
* Describe how adverse events will be followed until resolved or considered stable. Specify procedures for reporting and follow-up of AEs. Include duration of follow-up for appearance of AEs (e.g., one week, two months)
* Include details of the protocol-specific reporting procedures (individual responsible for each step (e.g., the Investigator, the Medical Monitor, etc.), how decisions will be made regarding determining relatedness and grading severity, which forms should be completed, how reports will be distributed)
* Completion of a Serious Adverse Event report form and specify specific information on where to send this form

## Site Monitoring Plan

Site monitoring is conducted to ensure the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH and regulatory guidelines.

General description of site monitoring: who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

## Data Quality Assurance

* Quality assurance and quality control systems implemented to assure the quality of the data (If none were used, this should be stated).
* Documentation of methods used in Appendix (e.g. monitoring, …)
* Audit procedure (documentation and audit certificates in Appendix)

## Statistical Analysis

* Reasons for the sample size selected, power of the study, level of significance to be used
* Describe planned analyses, comparisons and statistical tests
* Reasons for excluding subject from an analysis
* Planned monitoring of the results
* Frequency and nature of interim analyses

## Changes in the Conduct of the Study or Planned Analyses

E.g. removal of a treatment group, changing entry criteria, changing dose

* Give timing and reason for the change
* Give implications for result interpretation

## Protocol Amendements

If amendments to the protocol (modifying sense or objectives or modifying the undergone constraints or the risks incurred by the subjects) turn out to be necessary, they will be subjected at first opinion of the promoter of the study. After agreement by the promoter, these amendments will then be submitted to the opinion of the EC having examined the initial protocol.

# Study patients

## Disposition of patient

* Clear accounting of all patients who entered the study (e.g. randomized, completed the study, screened, discontinued, …)
* Give reasons for discontinuation
* State whether blind was broken for discontinued subject

## Protocol Deviations

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment should be described

## Data Management Responsibilities

The protocol should provide information on how the data will be managed, including data handling and coding for computer analysis, monitoring and verification (see point 8.9).

Instructions concerning the recording of study data on case report forms (paper CRF, eCRF).

# Finance and Insurance

Describe financing and insurance arrangements:

* Insurance without fault (Law of 7 May 2004)
* Financial agreement between the Sponsor, the investigator and the Institution to which it belongs :
	+ Specific information to trials without direct individual benefit
	+ Data protection
	+ Conflict of interests

Details of the research funding and any cost which will be incurred should be detailed in the protocol, along with any per-participant or per-site payments.

Information about legal responsibilities and insurance must also be outlined.

# Dissemination of Results and Publication Policy

The protocol should specify not only dissemination of results in the scientific media, but also to the community and/ or the participants, and consider dissemination to the policy makers where relevant. Publication policy should be clearly discussed- for example who will take the lead in publication and who will be acknowledged in publications, etc.

# Archiving

Secure archiving of all documentation of the experiment (CRF, Informed Consent, Source document,…) during at least 20 years. Specify who archives, where and access conditions.

# Study Report

Deadline of writing final report, who will draft it and to whom it will be transmitted.

# Literature References

See for help:

Guidelines for reading literature reviews, Andrew D. Oxman, MD, Gordon H. Guyatt, MD, CMAJ, VOL. 138, APRIL 15, 1988.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1267776/pdf/cmaj00165-0027.pdf>

# Appendix

* Patient information and consent form
* Laboratory values and agreement
* Laboratory technics
* CRF / questionnaires
* Regulatory documents réglementaires (Insurance, EudraCT, famhp …)
* Other