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|  | **POLICY – MEDICAL DEVICE PROTOCOL TYPE** |
| N° : AAHRPP-DSQ-007 / REV  001 | N° ENGLISH VERSION : 224 |

***"Please do take into account that this is a translation of the original French version validated in the Quality Management System (QMS) of Cliniques universitaires Saint-Luc through the SharePoint PaCo GED. Therefore in case of doubt, differences, inconsistency or discrepancy in this English version, the French version shall prevail"***

1. Définition :

A document that gathers information about the study: background information, rationale, objectives, results, design, prespecified analysis, methodology, monitoring, safety and follow-up, recording of clinical investigation data. This document is called the clinical investigation plan or clinical investigation protocol.

This information may also be provided in other documents that must be referenced in the protocol (investigator's brochure, informed consent, research contract etc).

The content of a clinical investigation protocol and any amended version should include all of the topics listed below and a justification for each topic if it is not self-evident. The protocol should preferably be written in English to facilitate subsequent publication. This document contains both a French and an English version of the sample protocol.

1. Content

front page

* Title of the clinical investigation
* Protocol identification number
* Eudract / EUDAMED number (if known)
* Protocol version number and version date

Signature page

* Identification and complete contact information of the Investigators associated with the project (or list in annex).
* Declaration of confidentiality (AAHRPP-FORM-031) with respect to the information contained in the protocol. It will be signed upon first receipt of the protocol (AAHRPP-SOP-019, AAHRPP-SOP-020).
* Statement that the clinical investigation will be conducted in accordance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

General information

* Title of the clinical investigation
* Protocol identification number
* Eudract / EUDAMED number (if known)
* Protocol version number and version date
* If modified, date and number
* In case of modification, summary of the modification/revision history
* Full identification & contact details of the sponsor (institution)
* Full identification & contact details of the local representative (if foreign sponsor)
* Full identification & contact details of the principal investigator
* Full identification & contact details of the site(s) where the clinical investigation will take place
* Full identification & contact details of external organizations (such as central laboratories, contract research organizations, consultants or other subcontractors) involved in the clinical investigation.
* The various roles, responsibilities and qualifications of the investigators must be specified.
* At the bottom of the page, the version number and identification number of the protocol, the page number and the total number of pages on each page (except the first page).

Synoptic summary (one page)

* Title of the investigation
* Sponsor
* Principal Investigator
* Participating centers
* Study design
* Type of study and methodology
* Objectives of the study
* Pre-existing data (light)
* Purpose
* Number of patients
* Inclusion criteria
* Exclusion criteria
* Treatment plan
* Statistical evaluation
* A brief description of how the clinical investigation was funded and a brief description of the agreement between the sponsor and the site(s) should also be included.

Flow chart of visits and procedures

Table of contents

List of abbreviations

Identification and description of the investigational device

* Brief description of the device.
* Details of the device manufacturer.
* Model or type name or number, including software version and accessories, if any, allowing full identification.
* Description of how to ensure traceability during and after the clinical investigation, e.g., by assigning lot numbers or serial numbers.
* Intended use of the device in the proposed clinical investigation.
* Population and indications for use of the device.
* Detailed description of the device, including all materials that will be in contact with tissue or body fluids. The description should detail all drug substances, human or animal tissues or their derivatives, or other biologically active substances and mention compliance with applicable national regulations.
* Summary of training and experience required for use of the device, taking into account risk assessment.
* Description of the medical or surgical procedures specific to the use of the device.
* References to the investigator's brochure and instructions for use.

The above information should also be provided, where possible, for the comparator where applicable.

justification for the design of the clinical investigation

* Assessment of the results of relevant preclinical trials/analyses and prior clinical investigations, if any, conducted to justify the use of the device in human subjects.
* References to literature and data relevant to the clinical investigation and serving as background information for the proposed clinical investigation.

Benefits and risks

* Expected adverse effects of the device.
* Risks associated with participation in the clinical investigation.
* Steps taken to control or mitigate the risks.
* Expected clinical benefits.
* Justification of the benefit/risk ratio

Objectives and hypotheses

* Purpose of the clinical investigation, statements regarding the clinical performance, efficacy or safety of the device under investigation to be verified.
* Objectives, primary and secondary, described in terms of "superiority", "non-inferiority" or "equivalence", if applicable.
* Scientific rationale and clinical relevance regarding magnitude of effects, margins of non-inferiority or limits of equivalence, if applicable.
* Primary and secondary assumptions, if any.
* Expected risks and adverse effects of the device, which should be evaluated.

The objective(s) should address the purpose of the clinical investigation and should relate to the hypotheses (if any) and corresponding endpoints relevant to the target population. The objectives of the clinical investigation should translate directly into the pre-specification andimplementation of the primary endpoint(s). Statements should be linked to eligibility criteria for the subject and users.

Design of the clinical investigation

General description

* Type of clinical investigation to be conducted (e.g., randomized, blinded or open-label, parallel or crossover, multicenter, international), the control group (e.g., comparative statement and reversible treatment of a chronic condition), and the comparator, with rationale and justification for choice.
* Description of the development phases of the device.
* Number of medical devices and comparators (if any) used per subject.
* Follow-up provided and expected duration (total and per subject) of the study. Justification for the duration of follow-up is recommended.
* Details of measures taken to minimize bias
* Definition of the end of the clinical investigation.

Study subjects

* Number of subjects
* Selection criteria (inclusion and exclusion)
* Representativeness of the study population in relation to the target population
* Vulnerable subjects involved (if applicable)
* Recruitment procedures
* Procedures for withdrawal and/or replacement of subjects, if applicable
* Estimated time required to recruit the expected number of subjects

Procedures

* Clinical procedures and diagnostic tests used during the clinical investigation and any deviations from standard clinical practice.
* Activities performed by the sponsor's representatives.
* Any known or foreseeable factors that may compromise the results of the clinical investigation or the interpretation of the results. For example, any comparator or other device or drug used, and therefore any concomitant authorized or prohibited treatments, but also subject factors such as age, sex, lifestyle.
* The methods for considering these factors in the clinical investigation, for example by the choice of subjects, by the design of the clinical investigation (such as stratified randomization) or by the statistical analysis, should be described.
* The follow-up period of the clinical investigation must be adequate to demonstrate clinical performance, efficacy or safety over a period of time sufficient to represent a realistic trial of the device and to allow identification and assessment of the risks associated with any adverse effects of the device.
* The specific and appropriate medical care to be provided to subjects after completion of the clinical investigation, if any.
* Recommended follow-up of subjects after completion of the clinical investigation.

The extent and nature of follow-up activities for the successful completion of the investigation in accordance with the clinical investigation plan should be described and, in accordance with Section 72 of the MDR, should be based on the objective(s), methodology, and degree of deviation of the intervention from normal clinical practice. Overall, the study should be designed to minimize pain, discomfort, fear, and any other possible foreseeable risks to subjects. For this, a rationale in relation to the available preclinical data and the results of the clinical evaluation may be recommended.

Monitoring plan

The clinical investigation plan should outline the monitoring plan to be followed, including access to source data and the expected extent of verification of source data, by the sponsor and/or regulatory authorities, in confidence.

Statistical design and analysis

The description and justification of the statistical model and analysis of the clinical investigation should cover the following

* Analysis population (e.g., intention-to-treat [ITT], per-protocol [PP], and actual treatment [AT] analysis) and procedures considering the data set.
* Descriptive statistics of baseline, treatment, safety data, and, where appropriate, primary and secondary endpoints.
* Analytical procedures including measures of precision, such as confidence intervals, where appropriate.
* Significance and power of primary endpoint(s) and, if applicable, overall statistical verification strategy.
* Sample size calculation and justification considering:
* all relevant clinical data on the outcome variable and effect size, if applicable;
* expected outcome assumptions in treatment groups, if any;
* adjustments due to pre-planned interim analyses, if any
* the magnitude of detectable effects and the non-inferiority margin, which should be less than the magnitude of detectable effects and justified relative to the comparator effect, if applicable
* the allocation ratio used for randomization (e.g., 1:1, 1:2), if applicable
* the expected dropout rate, such as withdrawal, loss of sight, death (unless death is an endpoint).
* All statistical parameters and methods used to calculate the sample size or non-inferiority margin should be clearly stated.
* Exploratory and sensitivity analysis (e.g., to test the robustness of the results of the primary and secondary analyses to the different methods used to deal with missing data), if applicable.
* Procedures for reporting deviations from the original statistical analysis plan.
* In the case of multicenter clinical investigations, a strategy for managing potential imbalances in enrollment at different investigative sites.
* Strategy for pooling data, if appropriate.

Data management

* Methods for data entry and collection.
* Describe the methods for archiving the data (N.B. according to Belgian law: data to be kept for a minimum of 20 years after the study is stopped: AR of 18 May 2006 article 24).

In accordance with Article 72 of the MDR, all information related to the clinical investigation must be recorded, processed, handled and stored by the sponsor or investigator, as the case may be, in such a way that it can be accurately reported, interpreted and verified, while preserving the confidentiality of the recordings and of the personal data of the subjects, in accordance with the applicable legislation on personal data protection. In addition, appropriate technical and organizational measures must be in place to protect the processed information and personal data from unauthorized or unlawful access, disclosure, dissemination, alteration or destruction, or accidental loss, especially when the processing involves transmission over a network.

Amendments

The clinical investigation plan must include a description of the procedures for amending the plan.

Deviations from the clinical investigation plan (deviation, violation)

* A statement that the investigator is not permitted to deviate from the clinical investigation plan. Except if to protect the rights, safety and well-being of human subjects under emergency circumstances may the investigator deviate without prior approval of the sponsor.
* Procedures for recording, reporting, and analyzing deviations from the clinical investigation plan.
* Reporting requirements and timelines.
* Corrective and preventive actions and criteria for disqualification of the principal investigator.

Device accountability

* Description of device accountability procedures.
* Procedures, specific materials and instructions for the safe return of devices under investigation, including potentially hazardous devices.

Statements of compliance

* Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles set forth in the Declaration of Helsinki.
* Statement specifying compliance with this document and with the national and European legislation.
* Statement specifying that the clinical investigation should not begin until the required approval/favorable opinions of the ethics committee and regulatory authority, if any, have been obtained.
* Statement specifying that any additional requirements imposed by the ethics committee or regulatory authority must be met, if applicable.
* Statement specifying the type of insurance provided to subjects, if applicable. Provide contact information for the insurer and attach a copy of the certificate of insurance covering liability even without fault.
* Statement addressing the financing of the clinical investigation, including a description of the agreement between the sponsor and the investigative site(s) and, if applicable, with the investigator(s), if not covered by a separate agreement.

Informed consent process

* Procedure for informing the patient, for obtaining informed consent and for protecting vulnerable populations involved, if applicable.
* Anonymity of the subjects participating in the study: the protocol must specify that the identity and participation of the subjects in the experimentation, will remain strictly confidential in accordance with the European General Data Protection Regulation of April 27, 2016 (in application since May 25, 2018), the Belgian law of July 30, 2018 on the protection of privacy with regard to the processing of personal data, as well as the law of August 22, 2002 on the rights of patients. Personal data will be coded. Subjects will not be identified by name or in any other recognizable way in any of the records, results or publications related to the experimentation.

Vulnerable population (if applicable)

* Description of the vulnerable population to be included in the clinical investigation.
* Description of the screening process to identify and protect vulnerable populations.
* Description of the specific process for obtaining informed consent.
* Description of the specific responsibility of the ethics committee.
* Description of any medical care provided to subjects after the clinical investigation is completed.

Adverse events, adverse device effects and device deficiencies

* Definitions of adverse events and adverse device reactions.
* Definition of device defects.
* Definitions of serious adverse events including serious health hazard, serious adverse device reactions and, if applicable, unexpected serious adverse device reactions.
* List of reportable adverse events, if any, including rationale.
* Timelines for reporting by the principal investigator of all adverse events and device defects to the sponsor and, if applicable, to ethics committees and the regulatory authority.
* Details of the adverse event reporting process, including date of event, treatment, resolution, assessment of severity and relationship to the device under investigation, and related procedure.
* Details of the process for reporting device defects.
* List of foreseeable adverse events and expected adverse effects of the device, their likely impact, means of mitigation or treatment.
* Emergency contact information for reporting serious adverse events and serious adverse device reactions.
* For Belgium, specify that SAEs are reported to the FAMHP via the Clinical Investigation Summary Safety Report Form and sent to the R&D division of the FAMHP, either by e-mail to ct.rd@fagg-afmps.be or via the CESP, as desired.

End, suspension or premature termination of the clinical investigation

* Criteria and provisions for premature termination or suspension of the clinical investigation for the entire investigation or for one or more sites.
* Requirements for subject follow-up and continuing care, after termination or temporary suspension of the investigation, for follow-up of subjects who have withdrawn consent and for subjects who have been lost to follow-up.
* In addition, it should be clear in the clinical investigation plan that the competent authority will be informed of the end of the clinical investigation, and that a rationale will be provided in the event of temporary or early termination of the study.

Publication policy

* Statement that the clinical investigation will be recorded in a publicly accessible database.
* Statement that the results of the clinical investigation will be made available to the public.
* Statement indicating the conditions and time frame under which the results of the clinical investigation will be published, including the role of the sponsor and the criteria for authorship.

Bibliography

List of bibliographic references related to the clinical investigation