A.1 General

A.1.1 Introduction

This document specifies the content of a CIP. If the required information is written in other documentation, for example the IB, such documentation shall be referenced in the CIP and shall be made available on request.

A.1.2 Identification of the clinical investigation plan

a) Title of the clinical investigation.
b) Reference number identifying the specific clinical investigation, if any.
c) Version or date of the CIP.
d) Summary of the revision history in the case of amendments.
e) Version/issue number and reference number, if any, with the page number and the total number of pages on each page of the CIP.
f) Abbreviations and acronyms.

A.1.3 Sponsor

Name and address of the sponsor of the clinical investigation and information about funding source.

A.1.4 Principal investigator, coordinating investigator and investigation site(s)

a) Name, address, contact details and professional position of
   1. principal investigator(s),
   2. coordinating investigator, if appointed.
b) Name and address of the investigation site(s) in which the clinical investigation will be conducted.
c) Name(s) and address(es) of external organizations (such as core laboratories, CROs, consultants or other contractors) involved in the clinical investigation.

The different roles, responsibilities and qualifications of investigators shall be specified.

A.1.5 Overall synopsis of the clinical investigation

A summary or overview of the clinical investigation shall include all the relevant information regarding the clinical investigation design such as inclusion/exclusion criteria, number of subjects, duration of the clinical investigation, follow-up, objective(s) and endpoint(s).

NOTE It can be useful to include a flow chart showing the key stages of the clinical investigation or any other information that can be of value for the conduct of the clinical investigation.

A.2 Identification and description of the investigational device

a) Summary description of the investigational device.
b) Details concerning the manufacturer of the investigational device.
c) Name or number of the model/type, including software version and accessories, if any, to permit full identification.
d) Description as to how traceability shall be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers, or serial numbers.
e) Intended purpose of the investigational device in the proposed clinical investigation.
f) The populations and indications for which the investigational device is intended.
g) Description of the investigational device, including any materials, that will be in contact with

tissues or body fluids. This shall include details of any medicinal substances, human or animal tissues or their derivatives, or other biologically active substances and reference to compliance with applicable national regulations.

h) Summary of the necessary training and experience needed to use the investigational device based on risk assessment.
i) Description of the specific medical or surgical procedures involved in the use of the investigational device.
j) References to the IB and IFU.

A.3 Justification for the design of the clinical investigation

a) Justification for the design of the clinical investigation, which shall be based on the conclusions of the clinical evaluation, and shall comprise
b) an evaluation of the results of the relevant pre-clinical testing/assessment and prior clinical investigations, if applicable carried out to justify the use of the investigational device in human subjects,
c) an evaluation of clinical data that are relevant to the proposed clinical investigation,
d) a description of the clinical development stage, if appropriate.

A.4 Benefits and risks of the investigational device, clinical procedure, and clinical investigation

a) Anticipated clinical benefits.
b) Anticipated adverse device effects.
c) Risks associated with participation in the clinical investigation.
d) Possible interactions with concomitant medical treatments as considered under the risk analysis.
e) Steps that will be taken to control or mitigate the risks.
f) Rationale for benefit-risk ratio.

A.5 Objectives and hypotheses of the clinical investigation

a) The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified.
b) Objectives, primary and secondary, described as ‘superiority’, ‘non-inferiority’, or ‘equivalence’, if applicable.
c) Scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.
d) Primary and secondary hypotheses, if applicable.
e) Risks and anticipated adverse device effects that are to be assessed.

The objective(s) shall serve the purpose of the clinical investigation and shall relate to the hypotheses (where applicable) and corresponding endpoints relevant to the target population. The objectives of the clinical investigation shall translate directly into the pre-specification and operationalisation of the primary endpoint(s). Claims shall be linked to eligibility criteria for subject and users.

A.6 Design of the clinical investigation

A.6.1 General

a) Description of the design type of clinical investigation to be performed (e.g. randomized, blinded

or open-label, parallel groups or crossover, multicentre, international) the control group, (e.g. comparative claim and reversible treatment of a chronic state) and the comparator with rationale and justification for the choice.

Absence of control(s) shall be justified.

b) Description of the measures to be taken to minimize or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors.
c) Primary and secondary endpoints, with rationale for their selection and measurement. If applicable, composite endpoints, with rationale for their selection and measurement.
The primary endpoint shall be appropriate for the investigational device and should be clinically relevant.
d) Methods and timing for assessing, recording, and analysing variables.
e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration.
f) Any procedures for the replacement of subjects (generally, not applicable to randomized clinical investigations).
g) Investigation sites: number, location, and, if appropriate, differences in investigation site environment.
h) Definition of completion of the clinical investigation

A.6.2 Investigational device(s) and comparator(s)

a) Description of the exposure to the investigational device(s) or comparator(s), if used.
b) List of any other medical device or medication to be used during the clinical investigation if not already specified in the instructions for use.
c) Number of investigational devices to be used, together with a justification.

A.6.3 Subjects

a) Inclusion criteria for subject selection.
b) Exclusion criteria for subject selection.
c) Criteria and procedures for subject withdrawal or lost to follow-up
    1) when and how to withdraw a subject from the clinical investigation or stop the use of the investigational device,
    2) documentation of efforts to be made to trace subjects that are lost to follow-up and possible reasons,
    3) whether and how subjects are to be replaced.
d) Point of enrolment.
e) Point of randomization, if applicable.
f) Total expected duration of the clinical investigation.
g) Expected duration of each subject's participation.
h) Number of subjects required to be included in the clinical investigation, and where needed, anticipated distribution of enrolment among the participating investigation sites.
i) Estimated time needed to select this number (i.e. enrolment period).
j) Relationship of investigation population to target population.
k) Information on vulnerable, pregnant, and breastfeeding population, if applicable.

A.6.4 Procedures

a) Description of all the clinical investigation-related procedures that subjects undergo during the clinical investigation including any deviation from normal clinical practice.
b) Description of those activities performed by sponsor representatives (excluding monitoring).
c) Any known or foreseeable factors that can compromise the outcome of the clinical investigation or the interpretation of results.
d) The methods for addressing these factors in the clinical investigation, for example, by subject selection, clinical investigation design, such as stratified randomization, or by statistical analysis shall be described.
e) The follow-up period during the clinical investigation shall permit the demonstration of clinical performance, effectiveness or safety over a period of time sufficient to represent a realistic test of the investigational device and allow any risks associated with adverse device effects to be identified and assessed.
f) Address what specific medical care is appropriate to be provided for the subjects after the clinical investigation has been completed, if applicable.
g) Address recommended follow-up for the subjects after the clinical investigation has been completed.
h) Address the final disposition or potential future use of samples obtained from subjects, if applicable.

A.6.5 Monitoring plan

General outline of the monitoring plan to be followed, including access to source data and the extent of source data verification planned.
It is possible to provide a detailed plan for monitoring arrangements separately from the CIP.

A.7 Statistical design and analysis

With reference to A.5 and A.6, the description of and justification for statistical design and analysis of the clinical investigation shall cover the following.

a) Analysis population (e.g. intention-to-treat, per-protocol, as-treated) and procedures that consider all the data.
b) b) Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.
c) c) Analytical procedures including measures of precision such as confidence intervals, if applicable.
d) d) The significance level and the power of primary endpoint(s) and the overall statistical testing strategy, if applicable.
e) Sample size calculation and justification considering:
    1) all relevant clinical data on outcome variable and effect size, if applicable;
    2) assumptions of expected outcomes across treatment groups, if applicable;
    3) adjustments due to any pre-planned interim analyses, if applicable;
    4) detectable effect size and non-inferiority margin, which shall be smaller than the detectable effect size and justified with reference to the effect of the comparator, if applicable;
    5) randomization allocation ratio (e.g. 1:1, 1:2), if applicable;
    6) expected drop-out rate, such as withdrawal, lost to follow-up, death (unless death is an endpoint).

f) The rationale for the number of procedures to be performed by a single user as part of the learning curve and how these data are to be analysed, if applicable.
g) Pass/fail criteria to be applied to the results of the clinical investigation.
h) The provision for an interim analysis, criteria for the termination of the clinical investigation on statistical grounds, where applicable.
i) Management of bias and, when randomization, matching, or blinding are applied, plan for assessment of success thereof.
j) Management of potential confounding factors (e.g. adjustment, stratification, or stratified randomization).
k) Description of procedures for multiplicity control and adjustment of error probabilities, if applicable.
l) The specification of subgroups for analysis, if applicable, or if response to treatment is expected to be different in these groups.
m) Management, justification, and documentation of missing, unused or spurious data, including drop-outs.
n) Exploratory analysis and sensitivity analysis (e.g. to explore robustness of results of primary and secondary analysis with respect to different methods used for handling missing data), if applicable.
o) Procedures for reporting any deviation(s) from the original statistical analysis plan.
p) For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.
q) A strategy for pooling data, if applicable.

A.8 Data management

a) Methods (e.g. CRF) for data entry and collection.
b) Procedures used for CRF tracking, data review, database cleaning, and issuing and resolving data queries. Specifically, timely, and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity, and reconciliation, if applicable, are necessary to ensure delivery of a quality database and the achievement of the clinical investigation objectives through the implementation of the planned analysis.
c) Procedures for verification, validation, and securing of electronic clinical data systems, if applicable.
d) Procedures to maintain and protect subject privacy.
e) Methods for database locking at the start of the analysis and storage upon completion of the clinical investigation.
f) Procedures for data retention.
g) Specified retention period.
h) Other aspects of clinical quality assurance, as appropriate.

A.9 Amendments to the CIP

Description of the procedures to amend the CIP.

A.10 Deviations from clinical investigation plan

a) Statement specifying that the investigator is not allowed to deviate from the CIP, except as specified in 5.6.4 c).

b) Procedures for recording, reporting, and analysing CIP deviations.
c) Notification requirements and time frames.
d) Corrective and preventive actions and principal investigator disqualification criteria.

A.11 Device accountability

a) Description of the procedures for the accountability of investigational devices as specified in 7.9; Procedures and particular materials and instructions for the safe return of investigational devices,
b) including those that are potentially hazardous.

A.12 Statements of compliance

a) Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
b) Statement specifying compliance with this document and any regional or national regulations, as appropriate.
c) Statement specifying that the clinical investigation shall not begin until the required approval/ favourable opinion from the EC and regulatory authority have been obtained, if appropriate.
d) Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.
e) Statement specifying the type of insurance that shall be provided for subjects, if appropriate.
f) Statement addressing the financing of the clinical investigation including a description of the agreement between the sponsor and investigation site(s), and where applicable with the investigator(s) if not addressed in a separate agreement.

A.13 Informed consent process

a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information and process for incentives for subjects, as needed.
b) Description of the informed consent process in circumstances where the subject is unable to give it; in the case of emergency treatment, the items specified in 5.8.3.4 shall be included.

A.14 Adverse events, adverse device effects, and device deficiencies

a) Definitions of adverse events and adverse device effects.
b) Definition of device deficiencies.
c) Definitions of serious adverse events including serious health threat and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects.
d) List of non-reportable adverse events, if applicable, including rationale.
e) Time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority.
f) Details of the process for reporting adverse events (date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the investigational device and the related procedure).
g) Details of the process for reporting device deficiencies.
h) List of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment.

i) Emergency contact details for reporting serious adverse events and serious adverse device effects.
j) Information regarding the DMC, if established.

A.15 Vulnerable population (if applicable)

a) Description of the vulnerable population to be included in the clinical investigation.
b) Description of the screening process to identify and protect the vulnerable population.
c) Description of the specific informed consent process.
d) Description of the EC's specific responsibility.
e) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

A.16 Suspension or premature termination of the clinical investigation

a) Criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites.
b) Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation, if the clinical investigation involves a blinding/masking technique.
c) Requirements for subject follow-up and continued care.

A.17 Publication policy

a) Statement that the clinical investigation will be registered in a publicly accessible database (see 5.4).
b) Statement indicating that the results of the clinical investigation will be made publicly available.
c) Statement indicating the conditions and timeframes under which the results of the clinical investigation will be offered for publication including the role of the sponsor and criteria for authorship.

A.18 Bibliography

List of bibliographic references pertaining to the clinical investigation.