Clinical investigation plan

The protocol of a medical device trial

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What is a CIP?

- A document that state(s) the
  - Rationale
  - Objectives
  - Design
  - proposed analysis
  - Methodology
  - Monitoring
  - Conduct
  - record-keeping
- of the clinical investigation

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Qualification

- All parties participating in the conduct of the clinical investigation shall be qualified by education, training or experience to perform their tasks

- This shall be documented appropriately

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CIP development

- The CIP and all subsequent amendments to the CIP are agreed upon between
  - the sponsor
  - all principal and coordinating investigators

- are recorded with a justification for each amendment.

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The contents of a CIP

- General
- Identification and description of the investigational device
- Justification for the design of the clinical investigation
- Risks and benefits of the investigational device and clinical investigation
- Objectives and hypotheses of the clinical investigation
- Design of the clinical investigation
- Statistical considerations
- Data management
- Amendments to the CIP
- Deviations from clinical investigation plan
- Device accountability
- Statements of compliance
- Informed consent process
- Adverse events, adverse device effects and device deficiencies
- Vulnerable population
- Suspension or premature termination
- Publication policy
- Bibliography

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1. General information

- Identification of the clinical investigation plan
- Sponsor
- Principal investigator, coordinating investigator and investigation site(s)
- Overall synopsis of the clinical investigation

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1.1: Identification of the CIP

- Title
- Reference number
- Version or date
- Summary of the revision history
- Page number and the total number of pages on each page.

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1.2: Sponsor

- Name and address of the sponsor of the clinical investigation.
  - If the sponsor is not resident in the country in which the clinical investigation is to be carried out, the name and address of a representative in that country can be required according to national or regional regulations.

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1.3: Investigators and site(s)

- Name, address, and professional position of principal and coordinating investigators
- Name and address of the investigation site(s)
- Name(s) and address(es) of other institutions involved

- The sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions.

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1.4: Overall synopsis

- 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).

- Useful to include a flow chart

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Figure. Example template of recommended content for the schedule of enrolment, interventions, and assessments.*

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	etc.	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
[List other procedures]	X							
Allocation		X						
INTERVENTIONS:								
[Intervention A]			◆—	—	—◆			
[Intervention B]			X		X			
[List other study groups]			◆—	—	—	—◆		
ASSESSMENTS:								
[List baseline variables]	X	X						
[List outcome variables]				X		X	etc.	X
[List other data variables]			X	X	X	X	etc.	X

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2. Investigational device

- Description of the device and its intended purpose.
- Details concerning the manufacturer
- Name or number of the model/type, including software version and accessories.
- How traceability shall be achieved
- Intended purpose in the investigation.
- The intended populations and indications
- Description of the device including any materials that will be in contact with tissues or body fluids.
- Necessary training and experience needed to use the device.
- The specific medical or surgical procedures involved in the use of the device.

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3. Justification for the design

- shall be based on the conclusions of the evaluation
  - an evaluation of the results of the relevant pre-clinical testing/assessment carried out to justify the use of the investigational device in human subjects
  - an evaluation of clinical data that are relevant to the proposed clinical investigation.

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4. Risks and benefits

- Anticipated clinical benefits.
- Anticipated adverse device effects.
- Residual risks associated with the investigational device
- Risks associated with participation in the clinical investigation.
- Possible interactions with concomitant medical treatments.
- Steps that will be taken to control or mitigate the risks.
- Risk-to-benefit rationale.
  - The risk management process, which includes risk analysis, risk-to-benefit assessment and risk control is described in ISO 14971.

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5. Objectives and hypotheses

- Primary and secondary objectives.
- Hypotheses to be accepted or rejected by statistical data from the clinical investigation.
- Claims and intended performance of the investigational device that are to be verified.
- Risks and anticipated adverse device effects that are to be assessed.

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6. Design of the clinical investigation

- General
- Investigational device(s) and comparator(s)
- Subjects
- Procedures
- Monitoring plan

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6.1: General

- Type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale
- The measures to be taken to minimize or avoid bias, including randomization and blinding/masking.
- Primary and secondary endpoints
- Methods and timing for assessing, recording, and analyzing variables.
- Equipment to be used for assessing the clinical investigation variables.
- Any procedures for the replacement of subjects.

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6.2: Investigational device(s) and comparator(s)

- Description of the exposure to the investigational device(s) or comparator(s)
- Justification of the choice of comparator(s).
- List of any other medical device or medication to be used during the clinical investigation.
- Number of investigational devices to be used, together with a justification.

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6.3: Subjects

- Inclusion criteria
- Exclusion criteria
- Criteria and procedures for subject withdrawal
- Point of enrolment.
- Total duration of the investigation.
- Duration of each subject's participation.
- Number of subjects required
- Time needed to select this number

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6.4: procedures

- All the clinical-investigation-related procedures that subjects undergo
- Activities performed by sponsor representatives (excluding monitoring).
- Any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results.
  - Baseline
  - Follow-up period
  - medical care

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6.5: Monitoring plan

- General outline of the monitoring plan to be followed
  - Access to source data
  - The extent of source data verification planned.

- It is possible to provide a detailed plan for monitoring arrangements separately from the CIP.

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7. Statistical considerations

- Statistical design, method and analytical procedures,
- sample size,
- the level of significance and the power
- expected drop-out rates,
- pass/fail criteria
- Interim analysis
- criteria for the termination of the investigation on statistical grounds,
- procedures for reporting any deviation from the original statistical plan,
- Subgroups for analysis,
- procedures that take into account all the data,
- The treatment of missing, unused or spurious data
- the exclusion of particular information from the testing of the hypothesis
- Multicenter clinical investigations: the minimum and maximum number of subjects to be included for each center.

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8. Data management

- Procedures used for data review, database cleaning, and issuing and resolving data queries.
- Procedures for verification, validation and securing of electronic clinical data systems, if applicable.
- Procedures for data retention.
- Specified retention period.
- Other aspects of clinical quality assurance, as appropriate

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9. Amendments to the CIP

- Description of the procedures to amend the CIP

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10. Deviations from CIP

- Statement specifying that the investigator is not allowed to deviate from the CIP
  - Emergency conditions
- Procedures for recording, reporting and analyzing CIP deviations.
- Notification requirements and time frames.
- Corrective and preventive actions and principal investigator disqualification criteria.

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11. Device accountability

- Description of the procedures for the accountability of investigational devices
  - the date of receipt,
  - identification of each investigational device (batch number/serial number or unique code)
  - the expiry date, if applicable,
  - the date or dates of use,
  - subject identification,
  - date on which the investigational device was returned/explanted from subject, if applicable
  - the date of return of unused, expired or malfunctioning investigational devices

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12. Statements of compliance

- Statement specifying that
  - the clinical investigation shall be conducted in accordance with the ethical principles
  - compliance with this International Standard and any regional or national regulations
  - the clinical investigation shall not begin until the required approval/favourable opinion from the EC or regulatory authority have been obtained.
  - any additional requirements imposed by the EC or regulatory authority shall be followed
  - the type of insurance that shall be provided for subjects

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13. Informed consent process

- Description of the general process for obtaining informed consent, including the process for providing subjects with new information, as needed.

- Description of the informed consent process in circumstances where the subject is unable to give it

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14. Adverse events, adverse device effects and device deficiencies

- List of foreseeable
  - Adverse events
  - Adverse device effects
  - Device deficiencies
- Serious or not?
- unanticipated or not?
- Time period for report
- Process for reporting.
- Emergency contact details for reporting

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15. Vulnerable population

- Description of the vulnerable population.
- Description of the specific informed consent process.
- Description of the EC's specific responsibility.
- Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed.

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16. Suspension or premature termination

- Criteria and arrangements
  - the whole clinical investigation
  - in one or more sites.
- Criteria for access to and breaking the blinding/masking code
- Requirements for subject follow-up.

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17. Publication policy

- Statement indicating whether the results of the clinical investigation will be submitted for publication.

- Statement indicating the conditions under which the results of the clinical investigation will be offered for publication.

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18. Bibliography

- List of bibliographic references pertaining to clinical investigation.

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Thank You!

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