Medical Device Regulation
Clinical evaluation and clinical investigations

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Clinical evaluation

- Confirmation of conformity with general safety and performance requirements (GSPR)
- Evaluation of undesirable side-effects and benefit/risk ratio
- Based on clinical data providing sufficient clinical evidence
- Manufacturer shall
  - specify and justify level of clinical evidence necessary to demonstrate compliance with GSPR
  - plan, conduct and document a clinical evaluation
- For class III and some Class IIb devices, manufacturer
  - may, prior to its clinical evaluation/investigation consult an expert panel to review the intended clinical development strategy and proposals for clinical investigation
  - shall give due consideration to views expressed by expert panel
  - these considerations shall be documented in clinical evaluation report
  - may not invoke any rights to views expressed by expert panel with regard to any future conformity assessment procedure

Clinical evaluation

- Establish and update a clinical evaluation plan
- Identify through a systematic scientific literature search
  - available clinical data relevant to the device and intended purpose
  - any gaps in clinical evidence
- Appraise the clinical data sets by evaluating their suitability for establishing the safety and performance of the device
- Generate any new or additional clinical data needed to address outstanding issues by properly designed clinical investigations
- Analyse all relevant clinical data to reach conclusions about safety and clinical performance or benefits of device
- Clinical evaluation
  - shall be thorough and objective, considering both favourable and unfavourable data
  - depth and extent shall be proportionate and appropriate to the nature, classification, intended purpose, manufacturer’s claims and risks of the device

Clinical evaluation plan

- Identification of general safety and performance requirements that require support from relevant clinical data
- Specification of
  - intended purpose of the device
  - intended target groups with clear indications and contraindications
- Detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters
- Specification of methods and parameters
  - examine qualitative and quantitative aspects of clinical safety with residual risks and side effects
  - determine acceptability of benefit risk ratio for various indications and intended purpose
- Indication of benefit/risk issues relating to specific components
- Clinical development plan
  - indicate progression from exploratory (first-in-man studies, pilot studies) to confirmatory investigations (pivotal clinical investigations)
  - PMCF with indication of milestones and description of potential acceptance criteria

Equivalence to the device

- Clinical evaluation can only be based on similar device clinical data
  - equivalence to the device in question can be demonstrated
  - technical, biological and clinical characteristics
- Technical
  - similar design
  - used under similar conditions of use
  - have similar specifications and properties (e.g. physicochemical properties such as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength, software algorithms)
  - use similar deployment methods
  - have similar principles of operation and critical performance requirements
- Biological
  - use same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact
  - similar release characteristics of substances, including degradation products and leachables

Equivalence to the device

- Clinical
  - used for the same clinical condition or purpose (including similar severity and stage of disease)
  - at the same site in the body
  - in a similar population (age, anatomy, physiology)
  - have same kind of user
  - have similar relevant critical performance according to the expected clinical effect for a specific intended purpose
- These characteristics shall be similar to such an extent
  - there would be no clinically significant difference in the clinical performance and safety of the device
- Considerations of equivalence must always be based on proper scientific justification.
- Manufacturers must be able to clearly demonstrate
  - they have sufficient levels of access to the data on devices to which they are claiming equivalence to justify that claimed equivalence.

Clinical evaluation report

- Clinical evaluation report
  - results of the clinical evaluation
  - clinical evidence supporting assessment of the conformity of the device
- Evidence
  - clinical evidence
  - non-clinical data generated from non-clinical testing
  - other relevant documentation
  - part of the technical documentation of the device in question
- Favourable and unfavourable data
  - part of the technical documentation.

Clinical evaluation

- Critical evaluation of relevant scientific literature relating to safety, performance, design characteristics and intended purpose
  - device subject to clinical evaluation is equivalent to existing device
  - data adequately demonstrate compliance with relevant general safety and performance requirements
- Critical evaluation of the results of all available clinical investigations
- Consideration of currently available alternative treatment options for that purpose
- In the case of implantable and class III devices, clinical investigations shall be performed, except if:
  - device has been designed by modifications of a device already marketed by the same manufacturer
  - modified device has been demonstrated by manufacturer to be equivalent to marketed device and this demonstration has been endorsed by NB
  - clinical evaluation of marketed device is sufficient to demonstrate conformity of modified device with relevant safety and performance requirements
  - NB shall check that PMCF plan is appropriate and includes post market studies to demonstrate safety and performance of the device

Class III MD exempt from clinical investigation

- MD demonstrated to be equivalent to already marketed device not made by the manufacturer, may be exempt from a clinical investigation if
  - two manufacturers have a contract in place that explicitly allows manufacturer of second device full access to technical documentation on an ongoing basis
  - original clinical evaluation has been performed in compliance with the requirements of this Regulation
  - manufacturer of the second device provides clear evidence thereof to NB
- Requirement to perform clinical investigations shall not apply to implantable devices and devices falling into class III
  - which have been lawfully placed on the market in accordance with Directive 90/385/EEC or 93/42/EEC and for which the clinical evaluation
    - is based on sufficient clinical data
    - is in compliance with relevant product-specific common specification for clinical evaluation of that kind of device
  - that are sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors for which clinical evaluation is based on sufficient clinical data and is in compliance with relevant product-specific common specification

Evaluation of products **without** medical purpose

- Clinical evaluations of these products shall be based on relevant data concerning safety
  - including data from post-market surveillance
  - specific post-market clinical follow-up
  - and, where applicable, specific clinical investigation
- For these products clinical investigations shall be performed unless it is duly justified to rely on existing clinical data from an analogous medical device.

Clinical evaluation update

- The clinical evaluation and its documentation
  - updated throughout the life cycle
  - with clinical data obtained from PMCF
- For class III and implantable devices
  - PMCF report and the summary of safety and clinical performance shall be updated at least annually with these data
- Clinical evaluation, its results and the clinical evidence
  - documented in a clinical evaluation report
  - part of the technical documentation

General requirements re clinical investigations

- Clinical investigations shall be designed, authorized, conducted, recorded and reported in accordance with the provisions of Articles 63-80 and Annex XV
- Establish and verify
  - that a device is designed, manufactured and packaged in such a way that it is
    - suitable for one or more of the specific purposes
    - achieves the performances intended as specified by its manufacturer
  - clinical benefits of a device as specified by its manufacturer
  - clinical safety of the device
- Determine any undesirable side-effects
- Assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device

General requirements re clinical investigations

- Clinical investigations shall be designed and conducted
  - the rights, safety, dignity and well-being of the subjects participating in a clinical investigation are protected and prevail over all other interests
  - the clinical data generated are going to be scientifically valid, reliable and robust
- Clinical investigations shall be subject to scientific and ethical review
  - The ethical review shall be performed by an ethics committee in accordance with the law of the MS concerned.
  - MS shall ensure that the procedures for the review by the ethics committees are compatible with the procedures set out in this Regulation
  - At least one lay person shall participate in the ethical review.

Legal representative of sponsor

- Where the sponsor of a clinical investigation is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative.
- Legal representative
  - responsible for ensuring compliance with sponsor's obligations pursuant to this Regulation
  - addressee for all communications with the sponsor
  - any communication to that legal representative shall be deemed to be a communication to the sponsor

Conditions for clinical investigation

- Clinical investigation subject to an authorisation by MS
- An independent ethics committee has not issued a negative opinion valid for that entire MS in accordance with its national law
- The sponsor, or its legal representative or a contact person is established in the Union
- Vulnerable populations and subjects are appropriately protected
- Anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored
- The subject or legally designated representative
  - has given informed consent
  - has been provided with the contact details of an entity where further information can be received in case of need
- The rights of subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded

Conditions for clinical investigation

- Clinical investigation
  - involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects
  - both the risk threshold and degree of distress are specifically defined in clinical investigation plan and constantly monitored
- Medical care provided to subjects is the responsibility of
  - an appropriately qualified medical doctor
  - any other person entitled by national law to the relevant patient care under clinical investigation conditions
- No undue influence, including that of a financial nature, is exerted on the subject, or on his or her legally designated representatives, to participate in clinical investigation
- The investigational device in question conforms to the applicable general safety and performance requirements apart from the aspects covered by the clinical investigation
- Every precaution to protect health and safety of subjects
  - technical and biological safety testing and pre-clinical evaluation
  - provisions in the field of occupational safety and accident prevention

Damage compensation

- Member States shall ensure
  - systems for compensation for any damage suffered by a subject resulting from participation in a clinical investigation are in place
  - insurance, a guarantee, or a similar arrangement
  - equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk
- Sponsor and the investigator shall make use of the system in the form appropriate for the MS concerned where the clinical investigation is conducted

Clinical Investigation Plan

- Clinical investigation plan (CIP)
  - define rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation
- Identification of the sponsor
  - name, address and contact details of the sponsor and, if applicable, the name, address and contact details of his contact person/legal representative
- Information
  - principal investigator at each investigational site, coordinating investigator
  - address details for each investigational site and emergency contact details for the principal investigator at each site
  - roles, responsibilities and qualifications of various kinds of investigators shall be specified in the CIP
- Brief description of financing of clinical investigation and agreement between the sponsor and the site
- Overall synopsis of the clinical investigation
- Risks and clinical benefits of device to be examined, with justification of corresponding specific clinical outcomes being used
- Description of relevance of the clinical investigation in the context of the state of the art of clinical practice

Clinical Investigation Plan

- Identification and description of the device
  - intended purpose, manufacturer, traceability, target population
  - materials coming into contact with the human body
  - medical or surgical procedures involved and necessary training and experience for its use
  - background literature search, the current state of the art in clinical care in relevant field of application and benefits of new device
- Objectives and hypotheses of the clinical investigation
- Design of the clinical investigation justifying scientific robustness and validity
  - General information such as type and phase of investigation with rationale for choice, endpoints, variables according to the CIP
  - Information on the investigational device, on any comparator and on any other device or medication to be used in clinical investigation
  - Information on subjects, selection criteria, size of investigation population and its representativity to target population, information on vulnerable subjects
  - Details of measures to be taken to minimise bias (e.g. randomisation) and management of potential confounding factors
  - Description of the clinical procedures and diagnostic methods related to the clinical investigation, highlighting any deviation from normal clinical practice.
  - Monitoring plan

Clinical Investigation Plan

- Statistical considerations, with justification, including a power calculation for the sample size
- Data management
- Information about any amendments to the CIP
- Policy regarding follow up and management of any deviations from CIP at investigational site and clear prohibition of use of waivers from CIP
- Accountability regarding the device
  - control of access to the device, follow-up in relation to the device
  - return of unused, expired or malfunctioning devices
- Statement of compliance with the recognised ethical principles for medical research involving humans
- Principles of good clinical practice in the field of clinical investigations of MD and applicable regulatory requirements
- Description of the Informed consent process
- Safety reporting including definitions of adverse events and serious adverse events, device deficiencies, procedures and timelines for reporting

Clinical Investigation Plan

- Criteria and procedures
  - follow up of subjects in case of the end, halt or early termination of an investigation, withdrawal of consent of subjects and subjects lost to follow up
  - procedure should at least include traceability of implantable device
- A description of the arrangements for taking care of the subjects after their participation in clinical investigation has ended
  - where such additional care is necessary because of the subjects' participation in the clinical investigation
  - where it differs from that normally expected for medical condition in question
- Policy as regards
  - establishment of the clinical investigation report
  - publication of results in accordance with the legal requirements
  - ethical principles
- List of the technical and functional features of medical device
  - indicating those that are covered by the investigation
- Bibliography.

Other information

- A signed statement by the natural or legal person responsible for the manufacture of the investigational device that device in question
  - conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the subject
- Copy of the opinion of the ethics committee concerned
- Proof of insurance cover or indemnification of subjects in case of injury
- Documents to be used to obtain informed consent, including the patient information sheet and the informed consent document
- Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data
  - organisational and technical arrangements that will be implemented to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed
  - description of measures that will be implemented to ensure confidentiality of records and personal data of subjects
  - description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects
- Full details of the available technical documentation
  - detailed risk analysis/management documentation or specific test reports shall upon request be submitted to the CA reviewing an application

Other sponsor’s obligations

- Sponsor shall have an agreement in place to ensure that the serious adverse events or any other event are reported by the investigator(s) to the Sponsor in a timely manner
- Documentation
  - sponsor shall undertake to keep available for CA any documentation necessary
  - shall be kept for a period of time of at least ten years after the clinical investigation with the device in question has ended
  - when the device is subsequently placed on the market, at least ten years after the last device has been placed on the market
  - In the case of implantable devices the period shall be at least 15 years
  - Each MS shall make provision that documentation is kept at the disposal of the CA in case the sponsor, or his contact person or legal representative established within its territory goes bankrupt or ceases its activity prior to the end of this period
- Sponsor
  - shall appoint a monitor that is independent from the investigational site to ensure that the investigation is conducted in accordance with the CIP, the principles of Good Clinical Practice and this Regulation
  - shall complete the follow up of investigation subjects
  - shall provide evidence to assure that the investigation is being conducted in line with Good Clinical Practice, for instance through internal or external inspection

Investigator’s Brochure

- Contain the clinical and non-clinical information on the investigational device
  - Any updates to the brochure or other relevant information that is newly available shall be brought to the attention of investigators in a timely manner
- Identification and description of the device
  - information on the intended purpose, the risk classification and applicable classification rule
  - design and manufacturing of device and reference to previous and similar generations of the device.
- Manufacturer's
  - instructions for installation, maintenance, maintaining hygiene standards and use,
  - storage and handling requirements, as well as the label and instructions for use.
  - information relating to any relevant training required

Investigator's Brochure

- Pre-clinical evaluation based on relevant pre-clinical testing and experimental data,
  - design calculations, in vitro tests, ex vivo tests, animal tests, mechanical or electrical tests, reliability tests, sterilisation validation
  - software verification and validation, performance tests, evaluation of biocompatibility and biological safety
- Existing clinical data
  - relevant scientific literature available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of the device and/or of equivalent or similar devices
  - relevant clinical data available relating to the safety, performance, clinical benefits to patients, design characteristics and intended purpose of equivalent or similar devices of the same manufacturer, including length of time on the market and a review of performance, clinical benefit and safety related issues and any corrective actions taken
- Summary of the risk/benefit analysis and the risk management
  - known or foreseeable risks, any undesirable effects, contra-indications and warnings

Investigator's Brochure

- In the case of devices that incorporate a medicinal substance, including a human blood or plasma derivative, or devices manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives
  - detailed information on the medicinal substance or on tissues or cells
  - compliance with relevant general safety and performance requirements and the specific risk management in relation to the substance or tissues, cells or their derivatives
  - substantiation of added value of incorporation of these constituents to the clinical benefit and/or safety of the device.
- A list detailing the fulfilment of the relevant general safety and performance requirements
  - standards and Common Specifications applied, in full or in part
  - description of the solutions for fulfilling relevant general safety and performance requirements
- A detailed description of clinical procedures and diagnostic tests used in the course of investigation and in particular information on any deviation from normal clinical practice

Application for clinical investigations

- Sponsor of clinical investigation shall submit through electronic system
- Electronic system shall generate a Union-wide unique single identification number for this clinical investigation which shall be used for all relevant communication
- Within ten days after receipt of application, MS shall notify the sponsor
  - whether clinical investigation falls within scope of this Regulation
  - whether application is complete
- Where the MS finds that the clinical investigation applied for does not fall within the scope of this Regulation or that the application is not complete
  - it shall inform the sponsor thereof and shall set a maximum of ten days for the sponsor to comment or to complete the application
  - MS may extend this period with a maximum of 20 days
- Where the sponsor has not provided comments nor completed the application within the time-period, the application shall be deemed to have lapsed
  - where the sponsor considers the application does fall under the scope of the regulation and/or is complete but the CA does not, the application shall be considered as rejected.
  - MS shall provide for an appeal procedure in respect of such refusal

Application for clinical investigations

- The MS shall notify the sponsor within five days following receipt of the comments or of the requested additional information
  - whether the clinical investigation is considered as falling within the scope of this Regulation and the application is completed
- In the period during which the application is being assessed the MS may request additional information from the sponsor
- Within one week of any change occurring in relation to the documentation
  - sponsor shall update the relevant data in the electronic system
  - MS shall be notified of update and changes to documents shall be clearly identifiable
- The Commission shall be empowered to adopt delegated acts amending or supplementing
  - in the light of technical progress and global regulatory developments
  - requirements for the documentation to be submitted with the application for the clinical investigation
- The Commission may adopt implementing acts
  - assure the uniform application of requirements for documentation to be submitted with the application for the clinical investigation
  - resolve issues of divergent interpretation and practical application

Clinical investigation application form

- Brief description of the investigational device, its classification and other necessary information
- Information as to whether the device incorporates a medicinal substance, including a human blood or plasma derivative, or whether it is manufactured utilising non-viable tissues or cells of human or animal origin, or their derivatives
- Summary of the clinical investigation plan (objective(s) of the clinical investigation, number and gender of subjects, criteria for subject selection, subjects under 18 years of age, design of the investigation such as controlled and/or randomised studies, planned dates of commencement and of completion of the clinical investigation).
- Information regarding a comparator device, its classification and other information necessary for the identification of the comparator device
- Evidence from the sponsor that the clinical investigator and investigational site are capable of conducting clinical investigation in accordance with CIP
- Details of the anticipated start date and duration of the investigation
- Details to identify NB
- Confirmation that the sponsor is aware that CA may contact the ethics committee that is assessing or has assessed the application

Clinical investigation application form

- Name, address and contact details of the sponsor and name, address and contact details of his contact person or legal representative
- Name, address and contact details of the manufacturer of the device intended for clinical investigation and AR
- Title of the clinical investigation
- Status of the clinical investigation application (i.e. first submission, resubmission, significant amendment)
- Details/reference to the Clinical Evaluation Plan
- If resubmission with regard to same device
  - previous date(s) and reference number(s) of earlier submission(s)
  - in the case of significant amendment, reference to the original submission
  - sponsor shall identify all of the changes from the previous submission together with a rationale for those changes, in particular, whether any changes have been made to address outcomes of previous CA or Ethics Committee reviews
- If parallel submission for a clinical trial on a medicinal product, reference to the official registration number of the clinical trial
- Identification of the MS, EFTA countries, Turkey and third countries in which clinical investigation shall be conducted as part of multicentre/multinational study at the time of application

Assessment by Member States

- Compliance of investigational device with applicable general safety and performance requirements
  - every precaution to protect the health and safety of the subjects
  - assurance of technical and biological safety testing and pre-clinical evaluation
- Risk-minimisation solutions comply with harmonised standards or the equivalence
- Plausibility of measures planned for safe installation, putting into service and maintenance of investigational device
- Reliability and robustness of data generated in clinical investigation
  - statistical approaches, design of the investigation and methodological aspects (including sample size, comparator and endpoints)
- In the case of devices for sterile use
  - evidence of the validation of manufacturer's sterilisation procedures or information on reconditioning
  - sterilisation procedures which must be conducted by investigation site
- Demonstration of safety, quality and usefulness of any components of animal or human origin or of substances

Electronic system on clinical investigations

- To create single identification numbers for clinical investigations
- To be used as an entry point for
  - submission of all applications or notifications for clinical investigations
  - all other submission of data, or processing of data in this context
- Exchange of information relating to clinical investigations between the MS and between them and the Commission
- For information by the sponsor including the clinical investigation report and its summary
- For reporting on serious adverse events and device deficiencies and related updates

Start the clinical investigation

- In the case of investigational devices classified as class I or
- In the case of non-invasive devices classified as class IIa or IIb
  - immediately after the validation date of the application, and provided that the ethics approval is obtained
- In the case of investigational devices other than those referred to above
  - as soon as the MS has notified the sponsor of its authorisation and ethics approval is obtained
  - MS shall notify the sponsor of the authorisation within 45 days after the validation date
  - MS may extend this period by a further 20 days for the purpose of consulting with experts.

Conduct of a clinical investigation

- The sponsor and investigator shall ensure clinical investigation is conducted in accordance with approved CIP
- Sponsor shall adequately monitor the conduct of clinical investigation
- All clinical investigation information shall be recorded, processed, handled, and stored
  - can be accurately reported, interpreted and verified
  - confidentiality of records and personal data of subjects remain protected
- Appropriate technical and organisational measures shall be implemented to protect information and personal data
  - against unauthorised or unlawful access, disclosure, dissemination, alteration, destruction or accidental loss
- MS shall inspect on an appropriate level investigation site(s)
  - check that clinical investigations are conducted according to the requirements of this Regulation and to approved investigation plan
- The sponsor shall establish a procedure for emergency situations which enables the immediate identification and immediate recall of the devices used in investigation

Substantial modifications to a clinical investigation

- If the sponsor intends to introduce modifications to a clinical investigation
  - likely to have a substantial impact on
    - safety, health or rights of the subjects
    - robustness or reliability of clinical data generated by the investigation
  - he shall notify, within one week, by means of the electronic system
- The notification shall be accompanied by
  - an updated version of the relevant documentation referred to in Chapter II of Annex XV
  - changes shall be clearly identifiable
- MS shall assess substantial modification to clinical investigation
- Sponsor may implement the modifications at the earliest 38 days after notification, unless the Member State concerned has notified the sponsor of its refusal

Recording and reporting of adverse events

- The sponsor shall fully record any of the following:
  - adverse event identified in the clinical investigation plan as critical to the evaluation of the results of the clinical investigation according to the clinical investigation plan
  - serious adverse event
  - device deficiency that might have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
  - new findings in relation to any event referred to above
- The sponsor shall report to all MS where a clinical investigation is conducted without delay
  - a serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
  - a device deficiency that might have led to a serious adverse event if suitable action had not been taken, intervention had not occurred, or circumstances had been less fortunate
  - new findings in relation to any event referred to above

Clinical investigations

- Clinical investigations shall be performed on the basis of an appropriate CIP
  - reflecting the latest scientific and technical knowledge
  - defined in such a way as to confirm or refute the manufacturer's claims regarding the safety, performance and benefit/risk related to the device
  - investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions
  - the rationale for the design and chosen statistical methodology
- Proper
  - procedures
  - research methodologies
- Clinical investigations shall be performed according to evaluation plan
  - sufficient number of intended users
  - in a clinical environment that are representative of the intended normal conditions of use of the device in the target patient population

Clinical investigations

- All the appropriate technical and functional features of the device in particular those involving the safety and performance, and their effect on subject outcome
  - shall be appropriately addressed and examined by the investigational design
  - A list of the technical and functional features of device and related subject outcomes shall be provided
- The endpoints of the Clinical Investigation
  - shall address intended purpose, clinical benefits, performance and safety
  - be determined and assessed using scientifically valid methodologies
  - primary endpoint shall be appropriate to the device and clinically relevant
- Investigator shall have access to technical and clinical data regarding device
- Personnel involved in the conduct of an investigation
  - adequately instructed and trained in the proper use of the investigational device, CIP and good clinical practice
  - training shall be verified and where necessary arranged by the sponsor and documented appropriately
- The clinical investigation report, signed by the investigator, shall contain a critical evaluation of all the data collected during the clinical investigation, including negative findings

Clinical investigation report

- Cover/introductory page(s)
  - title of the investigation
  - the investigational device, the single identification number, the CIP number
  - details with signatures of the coordinating investigators and the principal investigators from each investigational site.
  - details of the author and date of the report
- A summary of the investigation shall include
  - title, purpose of the investigation,
  - description of the investigation, investigational design and methods used
  - results of the investigation and conclusion of the investigation
  - completion date of the investigation, and in particular details of early termination, halts or suspensions of investigations.
- Investigational device description, in particular clearly defined intended purpose
- Summary of serious adverse events, adverse device effects and device deficiencies and any relevant corrective actions.

Clinical investigation report

- Clinical investigation plan summary
  - objectives, design, ethical aspects
  - monitoring and quality measures
  - selection criteria, target patient populations, sample size, statistical plan (hypothesis/sample size calculation, analysis methods) and justification
  - treatment schedules, follow up duration, concomitant treatments
- Results of the clinical investigation
  - subject demographics
  - analysis of results related to chosen endpoints
  - details of subgroup analysis (with rationale and justification)
  - compliance to CIP, follow up of missing data and patients withdrawing/lost to follow up from investigation
- Discussion/Overall conclusions
  - safety and performance results, assessment of risks and clinical benefits
  - discussion of clinical relevance in accordance with clinical state of the art, any specific precautions for specific patient populations, implications for the investigational device, limitations of the investigation.