MDCG 2024-3

Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices

March 2024

This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission. The document is not a European Commission document and it cannot be regarded as reflecting the official position of the European Commission. Any views expressed in this document are not legally binding and only the Court of Justice of the European Union can give binding interpretations of Union law.

Table of contents

Abbreviations 4
1. Introduction 5
2. Purpose of the CIP 6
3. Content of the CIP 6
3.1. General 6
3.2. Identification and description of the investigational device 7
3.3. Benefits and risks of the investigational device, clinical procedures and clinical investigation 8
3.3.1. Benefits 8
3.3.2. Risks 9
3.3.3. Benefit-risk ratio 10
3.4. Relevance of the clinical investigation 10
3.5. Objectives and hypotheses 11
3.6. Design of the clinical investigation 11
3.6.1. General information such as type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan 11
3.6.2. Information on the investigational device and any comparator to be used in the clinical investigation. 12
3.6.3. Information on subjects, selection criteria, size of investigation population, representativeness of investigation population in relation to target population and, if applicable, information on vulnerable subjects involved such as children, pregnant women, immuno-compromised or elderly subjects. 12
3.6.4. Details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors. 13
3.6.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice. 13
3.6.6. Monitoring plan 14
3.7. Statistical design and analysis 15
3.8. Data management 16
3.9. Modifications of the CIP 16
3.10. Deviations from the CIP 17
3.11. Device accountability 17
3.12. Statements of compliance 17
3.13. Informed consent process 18
3.14. Adverse events, adverse device effects and device deficiencies 18
3.15. End, suspension, or premature termination of the clinical investigation 19
3.16. Arrangements for subjects following participation 20
3.17. Publication policy 20
3.18. Technical and functional features of the device 20
3.19. Bibliography 20

Abbreviations

ADE	Adverse Device Effect[1]
AE	Adverse Event[2]
CIP	Clinical Investigation Plan
DD	Device Deficiency
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EUDAMED	European Database on Medical Devices
IB	Investigator's Brochure
IFU	Instructions for use
ISO	International Organization for Standardization
MDCG	Medical Devices Coordination Group
MDR	Medical Devices Regulation, (EU) regulation 2017/45 on medical devices
SADE	Serious Adverse Device Effect[3]
SAE	Serious Adverse Event[4]
SIN	Single Identification Number

[1] An adverse device effect is any adverse event related to the use of an investigational medical device or a comparator if the comparator is a medical device.
[2] Defined in article 2(57) of the MDR.
[3] Any adverse device effect that has resulted in any of the consequences characteristic of a SAE.
[4] Defined in article 2(58) of the MDR.

1. Introduction

When a sponsor of a clinical investigation submits an application according to article 70(1) of the MDR, to the Member State(s) in which the clinical investigation is to be conducted, the application shall be accompanied by the documentation referred to in Chapter II of Annex XV of the MDR.

According to section 2 of Chapter I of Annex XV of the MDR, clinical investigations shall be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge, and defined in such a way to be able confirm or refute the manufacturer's claims regarding the safety, performance and aspects relating to the benefit-risk determination of devices. The clinical investigation shall include an adequate number of observations to guarantee the scientific value and validity of the conclusions. The procedures and research methodologies used to perform the clinical investigation shall be appropriate to the device under investigation.

Section 3 of Chapter II of Annex XV of the MDR describes the legally required content of the Clinical Investigation Plan (CIP). Further the sections 2.7 in chapter I, 3.12 chapter II as well as 4 and 6 in chapter III of Annex XV indicate that clinical investigations should be conducted in accordance with good clinical practice.

The international standard ISO14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations. This standard has a normative Annex A that outlines the content of a CIP. Adherence with the ISO 14155:2020 standard is strongly recommended as it is a useful resource for sponsors when planning and developing their clinical investigations, although it is not mandatory for clinical investigations conducted in accordance with MDR. Note that standards are regularly updated, and it is foreseen that this guidance will be updated accordingly.

When preparing the CIP, sponsors are encouraged to review the full details of the regulation as well as the standard. In case there are discrepancies between MDR and the standard, the legal requirements of the regulation takes precedence. The requirements of both the MDR and ISO14155:2020 as well as experience from the competent authorities have been used to develop this guidance document.

This guidance document is not legally binding. It has been developed following contribution from national competent authorities, industry and relevant stakeholders and it should therefore be recognised as best practice. It has been written to support sponsors developing their CIP by describing in greater detail what type of information is expected in the respective CIP sections, to pre-empt questions from the competent authorities during the assessment of the clinical investigation application. Moreover, a CIP with the appropriate content will be instrumental in the conduct of the clinical investigation.

The content of the CIP should be adapted based on the type of clinical investigation and the type and development stage of the investigational medical device. The legal requirements in Section 3 of Chapter II of Annex XV of the MDR must be addressed or indicated as “not applicable” with justification.

This guidance document uses section 3 of chapter II in Annex XV of the MDR as a starting point, and follows the numbering of the regulation, in order to facilitate cross referencing to the legal requirements. It is not intended to be a template for writing a CIP, and it is not mandatory to present the information in a CIP in the same order as they are mentioned in the MDR or in this guidance.

In combined studies of medical devices and pharmaceutical products, there is an obvious need to accommodate the legal requirements from several regulations, and thus the structure and content of the CIP may need to be adapted. However, sponsors need to be aware that the elements required by MDR need to be present in a combined CIP/study protocol, and this guidance is intended to be useful also in those situations.

2. Purpose of the CIP

The clinical investigation plan (CIP) shall set out the rationale, objectives, design methodology, monitoring, conduct, record-keeping, and the method of analysis for the clinical investigation. The CIP should be detailed enough to serve as a manual for investigators conducting the clinical investigation in a consistent manner across investigational sites and over time. Further, the CIP should allow the competent authorities and ethics committees to assess whether the clinical investigation has been designed in such a way that potential risks to subjects or third persons, after risk minimization, are justified when weighed against the clinical benefits to be expected. The CIP should also allow the assessment of whether the reliability and robustness of the data to be generated in the clinical investigation warrants the exposure of subjects to the investigational device and procedures described in the CIP.

3. Content of the CIP

Note that it is preferred for all necessary information to be included in the CIP. If part of the required information is provided in a separate document, it will be summarised and referenced in the CIP. The referenced documents must be submitted together with the CIP as part of the initial submission package accompanying the clinical investigation application.

3.1. General

The general introduction should include:

- The title of the clinical investigation.
- The CIP reference number(s)[5].
- Version and date of the CIP.
- A summary of the revision history in case of modifications.
- Abbreviations and acronyms.
- An overall synopsis of the clinical investigation. For detailed guidance regarding content of the synopsis, please refer to recommended template in Annex A of this guidance. Note that information provided in the synopsis should also be detailed in the body of the CIP, and that information which is mentioned more than once needs to be consistent throughout the document. Further, it may be useful to include a graphic flow chart describing the clinical investigation design.

Note the requirement in section 3.1, chapter II of Annex XV of the MDR to provide an overall synopsis of the clinical investigation in an official Union language determined by the Member

[5] The sponsor's unique identifier such as CIP code/number, as well as the CIV-ID (issued by competent authority from Eudamed2) or SIN (Single Identification Number – automatically generated when sponsors start to a draft application in EUDAMED).

State concerned. Sponsors are advised to check national requirements in this regard and provide one synopsis per language.

The name and contact details of the following should be stated:

- Sponsor.
- Legal representative (if applicable)[6].
- Principal investigator(s).
- Coordinating investigator(s) (if applicable).
- Investigational sites in which the clinical investigation will be conducted.
- Other organisations such as central laboratories, clinical research organisations etc. contracted by the sponsor as providers for the clinical investigation (if applicable).
- Manufacturer of investigational device.

The different roles, responsibilities and qualifications[7] of various kinds of investigators shall be specified. In larger or more complex study setups, there may be several levels, e.g. co-ordinating investigator, principal investigators, and members of the investigational site team. Further, in case of combination studies, responsibilities and qualifications need to be clearly described for the various investigators involved, e.g. investigators at clinical investigation sites where patients are recruited and treated, vs investigators at the analysing sites for a performance study.

To facilitate updates, the names and contact details of the principal investigator(s) and investigational sites can be listed in a separate document which is referenced in the CIP. Note that in this case, it will be necessary to describe and maintain a procedure where an updated list with names and contact details of sites is available to all investigators throughout the conduct of the clinical investigation to facilitate communication, in, for example, emergency situations.

A brief description of the following must also be included:

- how the clinical investigation is financed.
- the agreement between the sponsor and the site(s).

A brief description of the agreement between the sponsor and the manufacturer of the investigational device (if applicable) should be included.

The information about the agreements between parties may include for instance information about providing investigational device(s) to the site as well as arrangements regarding proprietary information and publications.

3.2. Identification and description of the investigational device

This section of the CIP should include the information listed below, as applicable. If appropriate, references to the Investigator's Brochure (IB) and/or Instructions for Use (IFU) can be made. In case a comparator device is used the information below should also be provided for the comparator.

- Summary description of the investigational device including its intended purpose in the clinical investigation as well as the populations and indications for which the investigational device is intended.

[6] The requirement for a sponsor to have a legal representative is described in article 62(2) of the MDR.
[7] Refer to Article 62(6) of the MDR, Section 10.2 of ISO 14155:2020 and national provisions regarding investigator qualifications.

- If there is a known difference between the device's intended purpose/indication/population in the clinical investigation (due to development stage, study design or other reasons) and the planned intended purpose when the device is/will be placed on the market, this difference should be clearly stated.
- If the device has already been CE-marked and placed on the market, it should be explained whether the intended purpose of the device in the clinical investigation is different from the intended purpose for which the device has been CE marked, or if it is to be further assessed within the scope of its intended purpose. This should be clearly specified.

- Sponsors are recommended to also include the information required by Section 3.18, chapter II Annex XV of the MDR in the device description, i.e. to list the technical and functional features of the device, with specific mention of those covered by the investigation. Please refer to section 3.18 of this document for further guidance.
- Details concerning the manufacturer of the investigational device.
- Name or number of the model/type, including software version and accessories, if any, to permit full identification.
- Description as to how traceability will be achieved during and after the clinical investigation, for example, by assignment of lot numbers, batch numbers or serial numbers.
- A detailed description of the investigational device, including a list of all materials which will be in contact with tissues or body fluids. Also, any medicinal substances, human or animal tissues or their derivates, or other biological active substances incorporated in the device must be defined.
- Summary of the necessary training and experience needed to use the investigational device based on risk assessment.
- Description of the specific medical or surgical procedures involved in the use of the investigational device.
- A background literature review should be presented.

3.3. Benefits and risks of the investigational device, clinical procedures and clinical investigation

3.3.1. Benefits

A description should be provided of the potential benefits of the proposed clinical investigation. This concerns the direct benefit(s) to the study subjects but may also cover the benefit(s) to others.

In particular, regarding the direct and indirect benefit(s) to the study subject, the following factors should be considered, individually and in aggregate:

a) type of benefit(s) and estimated magnitude of the benefit(s).
b) if possible, probability evaluation of the subject experiencing one or more benefits, or identification of subgroups more likely to experience a benefit.
c) duration of the benefit(s), i.e., how long the benefit can be expected to last for the subject.
d) medical necessity, if a medical device provides benefits or addresses needs unmet by other medical devices or therapies.

Benefit considerations should also include an assessment of whether another medical device or therapy could be used in substitution, and the availability of that other medical device or therapy.

It may be necessary to take regional differences in availability of alternatives into account, which could lead to benefit considerations that vary by region.

Benefit(s) to others include(s) benefits to caregivers, family members, health care personnel, and public health.

Other information providing useful context is appreciated and may include consideration of patient preference information (when available) characterizing the subjects' perspective on benefit, i.e., the value that the patients place on the use of the medical device, as well as information characterizing subjects' tolerance for risk.

Please note that there are specific requirements for vulnerable populations and subjects that there should be scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit (see article 64-66 and 68 of the MDR).

3.3.2. Risks

Identify all risks which participation in the clinical investigation will result in subjects being exposed to, whether related to the investigational device or clinical investigation procedures (i.e., risk characterization). Possible interactions with concomitant medical treatments have to be considered.

In particular, for risk characterization, the following should be considered, individually and in aggregate: types of risk (taking account of the study design as well), their likelihood (probability of occurrence) and duration along with the severity of harm.

Also consider the risk factors for health care personnel, family members or caregivers, if any. Also, consider the risks related to the interpretation of the study data. Specifically, the risk of drawing a false conclusion based on clinical data obtained, and the risks associated with data which are inconclusive or difficult to interpret should be considered.

Also describe how the risks are minimised (i.e., risk mitigation). It is not necessary to include specific mitigations for risks that are determined to be negligible due to a low probability of occurrence and low severity of harm. However, it is expected that all possible risks are identified.

Non-negligible identified risks should be reduced as far as possible by the following measures, and in the following priority:

- Risk elimination/reduction through safe design and manufacture of the device. This involves identifying device risks through pre-clinical testing and making changes in design or manufacturing in advance of the clinical investigation. Verification and validation of device design should be conducted prior to commencement of the clinical investigation application.
- Protective measures such as physical protective measures or alarms.
- Communication of safety information, contraindications and residual risks (e.g., through labelling or informed consent), training of health care professionals/investigational staff, optimizing communication between sponsor and the participating sites as well as sponsor optimizing the transfer of relevant information between the sites, communicating safety data and residual risks with ethics committee(s) and competent authority to determine if any additional subject protection measures are needed.

Any residual risks related to the device, or the investigation should be mitigated by safe clinical investigation design. Any non-negligible risks which remain following device design and are mitigated by protective measures or communication of safety information should be considered

in the clinical investigation design and mitigated further if possible. Examples of how clinical investigation design can contribute to risk mitigation:

- Designing the clinical investigation to be conducted in accordance with relevant international standards, consensus guidance, and good clinical practice.
- Performance of the study at specialised clinical sites only, with investigators meeting specific specialist criteria.
- Staged enrolment and interim pre-specified subject safety assessment.
- The use of pre-specified stopping rules.
- Enrolling a narrow study population with more favourable benefit-risk profile.
- Study oversight involving expert independent monitoring committees.
- Frequent monitoring visits to the site(s) ensuring accurate recording of AEs, including the timing and clinical context and a description of any medical interventions provided and the associated outcomes, as well as compliance with safety reporting requirements.

The risks listed should align, to a relevant extent, with the list of anticipated A(D)E, SA(D)E, DD with SADE potential as mentioned in section 3.14.

For CE-marked devices (including comparators) a brief summary of the post market surveillance data available is of relevance.

The CIP should describe how the risk threshold and the degree of distress is defined and constantly monitored throughout the investigation, as required by the MDR[8].

3.3.3. Benefit-risk ratio

Summarize the rationale for the benefit-risk ratio of the clinical investigation, taking into account the conditions stated in articles 62(3) and 62(4)e of the MDR. Overall, the investigation must be designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects. For that, a rationale in relation to the available preclinical data and results of clinical evaluation is recommended.

For clinical investigations carried out with vulnerable populations (incapacitated persons, minor, pregnant or breastfeeding women) clearly explain if the clinical investigation involves an expected direct benefit for the subject [9]). In case of a clinical investigation in an emergency situation[10], it should be explained if the clinical investigation will have the potential to produce a direct clinically relevant benefit to the subject. In addition, it must be justified that the clinical investigation poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the patient's condition.

3.4. Relevance of the clinical investigation

Describe the relevance of the clinical investigation in the context of the state of the art of clinical practice.

[8] Article 62(4)i of the MDR.
[9] Articles 64-66 of the MDR.
[10] Article 68 of the MDR.

The justification for the design of the clinical investigation should be based on the conclusions of the clinical evaluation[11]. Summarize the evaluation of the relevant pre-clinical testing/assessment and any prior clinical investigations, to justify the use of the investigational device in human subjects. (if applicable). Provide an evaluation of clinical data that are relevant to the proposed clinical investigation.

Describe where the clinical investigation fits into the clinical development of the device (i.e., is this a pilot study, a pivotal study or a post-market clinical investigation?). The informative Annex I in ISO 14155:2020 has information on clinical development stages.

3.5. Objectives and hypotheses

The purpose of the clinical investigation, claims for clinical performance, effectiveness or safety of the investigational device that are to be verified should be described.

- Objectives are to be identified as primary, secondary and exploratory as relevant. If applicable, describe whether 'superiority', 'non-inferiority', or 'equivalence' is to be demonstrated.
- Include scientific justification and clinical relevance for effect sizes, non-inferiority margins or equivalence limits, where applicable.
- Primary and secondary hypothesis, if applicable.
- 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 to the corresponding endpoints that shall be relevant to the target population.

The endpoints of the clinical investigation shall address the intended purpose, clinical benefits, performance and safety of the device. The endpoints shall be determined and assessed using scientifically valid methodologies. The primary endpoint shall be appropriate to the device, clinically relevant and should be evaluable.

3.6. Design of the clinical investigation

The design should be sufficiently detailed with evidence of its scientific robustness and validity.

3.6.1. General information such as type of investigation with rationale for choosing it, for its endpoints and for its variables as set out in the clinical evaluation plan

- Indicate the study type (e.g., exploratory, confirmatory).
- Define the primary and secondary endpoints, with rationale for their selection and measurement, highlighting the endpoints that address safety and/or performance, as well as clinical benefit(s) of the device. If applicable, composite endpoints[12], with rationale for their selection and measurement should be justified.
- For certain investigations, in particular early studies of new/high risk devices additional safety measures should be considered, such as close monitoring by the sponsor and

[11] For details on clinical evaluation, refer to article 61 and Annex XIV of the MDR. The sponsor should also consult relevant MDCG guidance documents and section 6.3 of ISO 14155:2020.
[12] Composite endpoint is a pre-specified combination of more than one endpoint.

independent safety monitor, and limiting the rate of enrolment (e.g.; the study design could include an evaluation of the first patient before next patient is treated, a phased approach, use of a run-in component).

- Indicate the expected duration of the investigation, for each subject's participation and the estimated total duration of the clinical investigation.

3.6.2. Information on the investigational device and any comparator to be used in the clinical investigation.

- Present the study arms, i.e. the investigational device (which was presented in detail as outlined above in section 3.2) versus any comparator (other device, medication, treatment modality or sham procedure) used. The choice of, or absence of, comparator, should be justified.
- In case of implantable devices, the sponsor should provide subjects with an implant card. The content of the card and a description of when and how it is provided should be addressed in the CIP, considering relevant aspects of article 18 of the MDR.

3.6.3. Information on subjects, selection criteria, size of investigation population, representativeness of investigation population in relation to target population and, if applicable, information on vulnerable subjects involved such as children, pregnant women, immuno-compromised or elderly subjects.

- Indicate the number of subjects: The planned total number of subjects, as well as the distribution between study arms if applicable.
- Specify if the clinical investigation will include vulnerable subjects[13] such as children, pregnant and breast-feeding women, incapacitated, immunocompromised or elderly subjects or other subjects which may be deemed vulnerable.
- List the subject selection criteria, (i.e. specify inclusion and exclusion criteria), and indicate who is responsible for determining subject eligibility (i.e. define role and qualification).
- Describe the recruitment procedures, including when a subject is enrolled and if applicable, specify the time point of subject randomisation (which may be different from the time of enrolment) in the clinical investigation.
- Note the requirement[14] to perform clinical investigations in a clinical environment that is representative of the normal conditions of use of the device in the target patient population.
    - Discuss the representativeness of the investigation population in relation to the intended target population. The design may include consideration of, and justification for, aspects such as disease aetiology, disease severity, gender, age (e.g. adult, paediatric) and other special patient populations as appropriate.
    - Discuss the type of investigation sites (e.g. specialized clinic, primary health care centre, manufacturer's custom built facility etc.) and differences in investigation site environments. Elaborate on why the selected sites are deemed appropriate for the conduct of the clinical investigation.
    - In multicentre/multinational studies it might be necessary to consider any expected differences in the standard of care or patient outcomes based upon the

[13] Article 62(4)(d), articles 64-68 as well as section 3.6.3 in chapter II, Annex XV of the MDR relate to vulnerable subjects.
[14] Section 2.4 in chapter I, Annex XV of the MDR.

geographic distribution of the intended patient or user populations. Discuss the impact and account for any local adaptations.

- Describe whether patients were or will be involved during the different phases of the clinical investigation, e.g. involvement in determining the objectives, assessing the burden of study participation for subjects or dissemination of the results.

3.6.4. Details of measures to be taken to minimise bias, such as randomisation, and management of potential confounding factors.

- Describe measures taken to minimize bias or avoid bias, such as randomization, concealment of allocation, blinding/masking, and management of potential confounding factors. Use of either single arm or (choice of) comparator or other (historically) controlled design and the concept of blinding and unblinding, or running open label need to be covered, with rationale and justification.
- Sham procedures (if any) need to be thoroughly justified, in particular if the procedures are invasive or burdensome, as exposing subjects to risk without the potential benefit of the device/intervention may be questionable from an ethical perspective.
- Be transparent about any potential conflicts of interest, and if they are present, how these shall be managed. In particular, it needs to be discussed how undue influence on subjects and evaluation of endpoints can be avoided, for example in situations where the device inventors are closely involved in the conduct of the investigation. To avoid bias in certain assessments an independent committee may be used to determine eligibility, classification of events, endpoint adjudication etc. (clinical events committee (CEC)).
- Further a data safety monitoring board (DSMB) or data monitoring committee (DMC) should be considered, and in appropriate situations, appointed to continuously monitor the emerging clinical investigation results and advice on the termination or progression of the study.
- If the clinical investigation involves a blinding/ masking technique, include criteria for who will get access to and is authorised to break the blinding/masking code, and the circumstances when this would occur.

3.6.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation and in particular highlighting any deviation from normal clinical practice.

- Describe all the clinical investigation -related procedures and diagnostic methods used in the clinical investigation. Any deviation from normal clinical practice should be highlighted. A tabular overview/schedule of events may be helpful to summarise the activities by visit, but it also needs to be clearly presented in detail what will have to be performed at which visit, in which order, how and by whom.
- The number of medical devices and comparators (if applicable) used per subject, and procedures to ensure safe use of the device need to be described, in particular in situations where the same device is used for several subjects.
- Methods and timing for assessing, recording, and analysing variables (such as adverse events, symptoms, parameters and/or results to be studied), including details on the equipment to be used for assessing the clinical investigation variables and arrangements for monitoring the maintenance and calibration of such equipment.
- Specify which biological samples are collected for the purpose of the clinical investigation, if any, and describe the arrangements to comply with the applicable rules for the collection, storage and future use of biological samples.

- Follow-up of subjects: 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.
- Any concomitant treatments permitted or prohibited should be explicitly stated (remember to consider contraindications and interactions not only for the investigational device but also for comparators and required concomitant treatments).
- If applicable, lifestyle restrictions such as contraception measures or diet restrictions should be described.
- Criteria and procedures for subject withdrawal or lost to follow-up: Describe when and how to withdraw a subject from the clinical investigation or stop the use of the investigational device, efforts to be made to trace subjects that are lost to follow-up and possible reasons, as well as information on whether and how subjects are to be replaced. It is recommended to consider the need for a last safety follow-up visit (if relevant for the clinical investigation and accepted by the subject) for subjects that withdraw from use of the device and/or other follow up activities defined in the CIP.
- Address whether the subjects can continue the use of the medical device once the clinical investigation has been completed, if applicable.
- Clinical investigations of implantable devices need to address procedures for explantation (including return and analysis of explants obtained at explantation or post-mortem examinations) and in situations where implants are left in situ, the monitoring of patient safety beyond the study period needs to be ensured.

3.6.6. Monitoring plan

The sponsor shall ensure adequate monitoring of the clinical investigation to verify that the rights, safety and well-being of subjects are protected, that the reported data are reliable, and robust, and that the conduct of the clinical investigation is in compliance with the requirements of MDR[15] and standard for good clinical practice (GCP).

The CIP shall contain information on the monitoring plan.[16] It is acknowledged that a detailed monitoring plan may not have to be provided with the application. The monitoring plan can be a separate document, as determined by the sponsor, but the CIP should include at least the following:

- A general outline of the monitoring plan.
- A description of the appointment of a monitor that is independent from the investigational site.
- A description of the monitor's access to source data and the extent of source data verification planned.

The extent and nature of monitoring the conduct of the investigation in accordance with the clinical investigation plan, good clinical practice and the MDR should be based on the characteristics of the clinical investigation, including objective(s) and methodology of the clinical investigation and degree of deviation of the intervention from normal clinical practice.

[15] Article 72(2) of the MDR.
[16] Section 3.6.6, chapter II, Annex XV of the MDR.

3.7. Statistical design and analysis

The CIP shall describe and justify the statistical design and analysis of the clinical investigation and should cover following points, if applicable:

- Analysis population and procedures that take into account all the data.
- Descriptive statistics of baseline data, treatments, safety data and where applicable, primary and secondary endpoints.
- Analytical procedures including measures of precision such as confidence intervals.
- With regards to the primary endpoint, the statistical testing strategy should be presented, if applicable, including the power calculation and the level at which statistical significance will be claimed.
- Sample size calculation and justification considering:
  - all relevant clinical data on the outcome variable and effect size, if applicable;
  - assumptions about expected outcomes in the treatment groups, where applicable;
  - adjustments due to pre-planned interim analyses, if any;
  - the magnitude of the detectable effects and the non-inferiority margin, which must be smaller than the magnitude of the detectable effects and be justified in relation to the comparator effect, if applicable;
  - the allocation ratio used for randomisation (e.g. 1:1, 1:2) if applicable;
  - the expected drop-out 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.

  For exploratory and observational clinical investigations, where sample size determination by calculation is not required per Annex I of the ISO14155:2020 standard, the scientific justification for the sample size selected should be provided.
- 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.
- Pass/fail criteria to be applied to the results of the clinical investigation.
- The provision for interim analyses, if applicable, and the provision of objective, quantifiable, statistical criteria for the termination of the clinical investigation[17].
- Management of bias and, when randomization, matching, or blinding are applied, plan of assessment of success thereof. Strategies to manage and control for potential confounding factors (e.g. stratified randomisation or stratification of the analysis). These strategies should be justified.
- For multicentre clinical investigations, a strategy for handling the potential imbalance of the numbers of subjects across investigation sites.
- Description of procedures for multiplicity control and adjustment of error probabilities.
- The specification and justification of subgroups for analysis, including specification of whether response to treatment is expected to be different in these groups.
- Management, justification, and documentation of missing, unused or spurious data, including drop-outs.
- 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).
- Procedures for reporting any deviations(s) from the original statistical plan.
- A strategy for pooling data, if applicable.

[17] There could also be non-statistical grounds for termination of a clinical investigation.

It is recommended to consult appropriate statistical expertise when designing the clinical investigation and writing the clinical investigation plan.

3.8. Data management

In the clinical investigation plan, a description should be provided of the procedures implemented which can guarantee that the data generated in the clinical investigation is reliable and robust. Present the arrangements to record, process, handle and store data in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection. Present post-collection procedures to check data accuracy and completeness, as well as procedures for issuing and resolving data queries and methods for data base locking at the start of the analysis.[18]

Throughout, and after the completion of, the clinical investigation, appropriate technical and organizational measures should be installed to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves transmission over a network.

The MDR specifically requires[19] that the application for a clinical investigation includes a description of measures that will be implemented in case of a data security breach in order to mitigate the possible adverse effects. The data management section of the CIP is a reasonable place to include this information, or a separate document can be included.

Also the data retention requirements as specified in section 3 of chapter III in Annex XV of the MDR should be addressed.

3.9. Modifications of the CIP

It should be clear from the clinical investigation plan that, the competent authority[20] shall be notified of all proposed changes to the approved clinical investigation that are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation, as required in Article 75 of the MDR. Also the CIP should inform the investigator of the need to wait for the time specified in article 75 of the MDR or for the approval of the substantial modification, whichever comes first, before implementing the changes.

The procedures to manage non-substantial modifications to the CIP also needs to be described.

[18] Refer to sections 6.6, 7.8 and A.8 of the ISO14155:2020 for additional guidance on data management aspects.
[19] last indent of section 4.5, chapter II in Annex XV of the MDR.
[20] Note that it may be necessary to take into consideration also national requirements in relation to submission of substantial modifications to the Ethics Committee.

3.10. Deviations from the CIP

There should be a statement specifying that the investigator is not allowed to deviate from the CIP, except if to protect the rights, safety and well-being of human subjects under emergency circumstances, when the investigator may deviate without prior approval of the sponsor.

It further needs to be clearly stated in the CIP that waivers from the CIP are not permitted.

Procedures for recording, reporting, and analysing CIP deviations should be described, including notification requirements and time frames. Also, corrective and preventive actions and principal investigator disqualification criteria are to be included.

3.11. Device accountability

Adequate procedures for the accountability and traceability of the investigational device should be incorporated in the CIP, in particular control of access to and adequate storage of the device, follow-up in relation to the device used in the clinical investigation and the return of unused, expired or malfunctioning devices.

Describe in detail how the use of the investigational device is restricted, so that they are used only in the clinical investigation and according to the CIP[21]. Specify that the investigator shall keep records to document

- name(s) of person(s) who received, used, returned, or disposed of the device.
- the date of receipt, identification, and quantity of each investigational device (batch number/serial number or unique code).
- the expiry date, if applicable; d) 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, if applicable.
- the date and documentation of disposal of the investigational devices as per instructions of the sponsor, if applicable.

3.12. Statements of compliance

The following statements should be included in the CIP:

- Statement specifying that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.
- Statement specifying compliance with any relevant international standards and/or consensus guidance, such as the latest version of the international standard ISO 14155 Clinical investigation of medical devices for human subjects – Good clinical practice[22]
- Statement specifying compliance with the national legislation and MDR.

[21] It may be acceptable to make exemptions regarding device accountability for those clinical investigations where CE marked devices are used within their intended purpose.

[22] If the sponsor chooses not to comply with this standard, it is necessary to demonstrate that the alternative solutions do ensure sufficient protection of the rights, safety and well-being of subjects, the scientific conduct of the clinical investigation and the credibility of the clinical investigation results at a level that is equal or superior to the methods specified in the standard.

- Statement specifying that the clinical investigation shall not begin until the required regulatory and ethical assessments have been completed with non-negative outcomes, in accordance with MDR and national legislation.
- Statement specifying that any additional requirements imposed by the Ethics Committee or regulatory authority shall be followed, if appropriate.
- Statement specifying the type of insurance that shall be provided for subjects, if appropriate.

3.13. Informed consent process

Describe the general process for obtaining informed consent, including the process for providing subjects with new information and process for compensation to subjects for participation in the clinical investigation, as needed. If applicable, the description of the process in circumstances where the subject is unable to give informed consent must also be included.

For clinical investigations on minors, the CIP must provide a summary of how it meets MDR Article (65) requirements, including the informed consent of the minor's legally designated representative, and the provision of information to the minor in a way that is adapted to their age and mental maturity.

For clinical investigations in emergency situations, it should be justified why and how the conditions in article 68 of the MDR, that allow inclusion of subjects and a first intervention without a prior informed consent, are considered to be fulfilled. Describe the planned procedures to identify a legally designated representative for such subjects to ensure that informed consent can be obtained without undue delay either from the legally designated representative or the subject, whichever can be done sooner. National legislation in appointing legally designated representatives differs. To ensure compliance with national provisions it is necessary for the sponsor to provide the investigators with appropriate guidance on how to proceed in their country. For multinational investigations, the information could be provided as a country specific appendix to the CIP.

3.14. Adverse events, adverse device effects and device deficiencies

List the definitions of adverse events (AE), adverse device effects (ADE), device deficiencies (DD), serious adverse events (SAE) and serious adverse device effects (SADE). Note the requirements for recording and reporting of adverse events in article 80 of the MDR, and consult the guidance document MDCG 2020-10/1 [23] for definitions and more information on the reporting of SAE and DD.

A list of foreseeable adverse events and anticipated adverse device effects, together with their likely probability of occurrence, mitigation, or treatment must be specified.

Should the sponsor wish to exclude some adverse events from recording and/or reporting, these should be listed, and a rationale provided for why they are to be considered non-reportable.

Details of the process for recording, follow-up and reporting adverse events and device deficiencies should be described, including the time frame which the principal investigator must report to the sponsor and, where appropriate, the sponsor must report to the competent

[23] MDCG 2020-10/1 Rev 1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745

authority. Emergency contact details for reporting SAE and SADE must be specified, so that the investigator knows whom to contact.

Information on the presence or absence of a data safety monitoring board/data monitoring committee[24] (DSMB/DMC) should be provided. In case of the absence of a DSMB/DMC, a justification should be provided.

3.15. End, suspension, or premature termination of the clinical investigation

Define the end of the clinical investigation. The end of investigation definition is important in relation to reporting requirements at the end of the study as outlined in article 77 of the MDR.

The clinical investigation plan should consider appropriate stopping criteria on both subject and study level. Consider that depending on the situation, it might be necessary to stop recruitment of new subjects and treatment of subjects currently exposed to the device, but also necessary to continue follow up of already treated/ implanted patients. Procedures should be described for the follow-up and continuing care of subjects following the end or temporary halt of the investigation. If applicable, procedures should be described for follow-up of subjects who have withdrawn their consent and for subjects lost to follow-up. For implantable devices it should be specified whether the devices are to remain implanted or be explanted at the end of the study and how traceability is achieved.

Include a description of any required follow-up (incl. the duration of such a follow-up period) of SAE with a causal relationship with the investigational device, still ongoing at the end of the clinical investigation, based on a risk assessment by the sponsor of the characteristics and properties of the investigation and the investigational device. This description should also include how any potential new SAEs that are detected during such follow-up are to be handled.

Further, it must be clear from the clinical investigation plan that the competent authority shall be notified of the temporary halt or (premature) end of the clinical investigation, and that a justification shall be provided in case of a temporary study halt or early termination. In accordance with MDR article 77 study (premature) end or temporary halt reporting is mandatory within 15 days (or 24 hours if based on safety grounds).

In addition, a clinical investigation report needs to be submitted to the competent authority[25] within one year of the end of the clinical investigation or within three months of the early termination or temporary halt. The clinical investigation report shall be accompanied by a summary presented in terms that are easily understandable to the intended user. Refer to the Commission Guidance on the content and structure of the clinical investigation report (2023/C 163/06).

[24] A data monitoring committee can be established by the sponsor to assess at intervals, the progress of the clinical investigation, the safety data or the critical clinical performance or effectiveness endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation. Sponsor can pre-empt requests for information from the competent authorities during the assessment of the clinical investigation application by submitting the DSMB charter with the initial application.

[25] Note that it may be necessary to consider also national requirements regarding reporting at the end of the clinical investigation which may include reporting to the Ethics Committee.

3.16. Arrangements for subjects following participation

Describe the arrangements for taking care of the subjects after their participation in the clinical investigation has ended, where such additional care is necessary because of the subjects' participation in the clinical investigation and where it differs from that normally expected for the medical condition in question.

3.17. Publication policy

Following statements must be included:

- Statement that the clinical investigation will be registered in a publicly available database[26].
- Statement indicating that the results of the clinical investigation will be made publicly available.
- 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.

3.18. Technical and functional features of the device

List the technical and functional features of the device and specify those features which are studied in the clinical investigation.

A tabular presentation of the relevant product characteristics of the investigational device is expected with an indication of the associated product specifications and assignment of the expected clinical outcome. Please, state the expected clinical performance outcomes specifically (e.g., according to the clinical investigation endpoints) and generally (whether it is a safety or performance characteristic).

Depending on the level of complexity, this information could be integrated with other sections, such as the device description and/or endpoint (refer to sections 3.2 and 3.6.1 above) or may need to be presented in a separate section.

3.19. Bibliography

List of bibliographic references relating to the clinical investigation.

[26] Once EUDAMED is fully functional, the clinical investigations will be registered there upon application, but until EUDAMED is fully functional, sponsors will have to register the clinical investigation elsewhere to be compliant with article 35 of the Declaration of Helsinki and section 5.4 of ISO14155:2020.

Appendix A: Clinical Investigation Plan Synopsis Template

Clinical Investigation Synopsis (Template)	
Title	[enter text here]
Short title	[enter text here]
Lay title, if applicable	[enter text here]
CIP number, version, and date	[enter text here]
EUDAMED Single Reference Number (SRN) or CIV-ID, if previously assigned	[enter text here]
CI modification number, if applicable	[enter text here]
Sponsor name and address	[enter text here]
Participating Location(s) and country(ies)	[enter text here]
Name of Investigational Device	[enter text here]
Clinical investigation Purpose and Background • Rationale for CI • Background of device and condition • Current standard of care	[enter text here]
Name of Comparator, if applicable	[enter text here]
Clinical development stage	[enter text here]
Design of the clinical investigation	[enter text here]
Objectives	[enter text here]
Primary endpoints	[enter text here]
Secondary endpoints	[enter text here]
Safety endpoints	[enter text here]
Exploratory / Other endpoints and outcomes	[enter text here]
Description of participants / study population	[enter text here]
Inclusion criteria	[enter text here]
Exclusion criteria	[enter text here]
Sample size	[enter text here]
Duration and follow up of the clinical investigation	[enter text here]
Statistical considerations	[enter text here]

Note: For combination studies, more details may be relevant, such as EU number of the clinical trial, name and description of investigational medicinal product or CIV-ID/SRN of performance study of an in vitro diagnostic device.