411.11 Checklist for evaluation of clinical investigation of medical devices with human beings according to EN ISO 14155:2012

Ref:	Device:	Date:

Manufacturer:				
Auditor:	Name		Signatu-re	

1. Scope

This checklist shall be used for audit of documentation of a design examination of medical devices of class Is, Im, IIa, IIb and III according to annex IX of the Council Directive 93/42/EEC.

DIN EN ISO 14155:2012 is not applicable for IVD medical devices.

2. Responsibilities and authorities

Product manager / Certification decision maker (93/42/EEC)

In line of this process the product manager and/or a certification decision maker shall choose the approved auditors/experts and assures about their qualification.

In case of any doubts during assessment, differing from the assessor guideline's requirements, the product manager and/or a certification decision maker as contact person for auditors share the responsibility for decisions related to the assessment, substituted and supported by the Business Sector representatives. If the Product Manager or Business Sector Representative acting as technical assessor, no further involvement as certification decision maker is possible.

3. Method of evaluation

When evaluating a technical file, the conformity to DIN EN ISO 14155:2012 shall be verified. For the verification the attached checklist shall be used. The results shall be stated in an appropriate report.

4. Further applicable documents

Device File Review

System Assessment

Pruefplan EGA

Report Design examination

Checklist Clinical Evaluation

Checklist Design Examination Annex II.4

Report Technical documentation approval on a representative Basis

5. Application of audit checklist

The rating of the documentation and of the implementation of the requirements shall be documented in the third column as follows:

1 = fully compliant
2 = partially compliant, still acceptable
3 = partially compliant, not acceptable
4 = non-compliant
na = not applicable

No.	*Quetion*	*Reference / Remark*	*Evaluation*
4. Ethical considerations			
4.1 General			
	Have clinical investigations been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki? Have these principles been understood, overserved, and applied at every step in the clinical investigation?		
4.2 Improper influence or inducement			
4.2.1	Has the sponsor avoided improper influence on, or inducement of the subject, monitor, any investigation(s) or other parties participating in, or contributing to, the clinical investigation?		
4.2.2	Have all investigators avoided improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation?		
4.3 Compensation and additional health care			
4.3.1	Has compensating subjects for costs, resulting from participation in the clinical investigation (e.g. transportation) been appropriate, if allowed by national regulations and hasn't the compensation been so large as to unduly encourage the subjects to participate?		
4.3.2	Have arrangements for additional health care been made and documented for subjects who suffer from an adverse event as a result of participating in the clinical investigation?		
4.4 Responsibilities			
	Have all parties involved in the conducts of the clinical investigation shared the responsibility for its ethical conduct in accordance with their respective roles in the clinical investigation?		
4.5 Communication with the ethics committee (EC)			
4.5.1 General			
	If national or regional EC requirements are less strict than the requirements of this International Standard, has the sponsor applied the requirements of this International Standard to the greatest extent possible, irrespective of any lesser requirements, and has he recorded such efforts?		
4.5.2 Initial EC submission			
4.5.2.1	Have the following information and any amendments been provided, as a minimum to the EC: a) CIP? b) IB or equivalent documentation? c) Informed consent form and any other written information to be provided to subjects? d) Procedures for recruiting subjects and advertising materials, if any?		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	e) A copy of the curriculum vitae (CV) of the principal investigator(s) for which the EC has oversight?		
4.5.2.2	Have the following documents also been provided to the EC depending on the clinical investigation design and national or regional requirements: f) Sample or drafts CRFs, including other data collection tools, as required by the CIP? g) Documents related to payments and compensation available to subjects? h) Proposed compensation to the institution or principal investigator? i) Documentation related to any conflict of interest, including financial, on the part of an investigator? j) Evidence of the clinical investigation insurance?		
4.5.3 Information to be obtained from the EC			
	Has the sponsor, prior to commencing the clinical investigation, obtained documentation of the EC's approval/favourable opinion identifying the documents and amendments on which the opinion was based?		
4.5.4 Continuing communication with the EC			
4.5.4.1	Has the following information been provided to the EC, if required by national regulations, the CIP or the EC, whichever is more stringent: a) serious adverse events; b) requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the clinical investigation?		
4.5.4.2	Under emergency circumstances, have deviations from the CIP been preceded without prior approval of the sponsor and the EC to protect the rights, safety and well-being of human subjects? Have such deviations been documented and reported to the sponsor and the EC as soon as possible? c) progress reports, including safety summary and deviations; d) amendments to any documents already approved by the EC; e) if applicable, notifications of suspensions or premature termination; f) if applicable, justification and request for resuming the clinical investigation after a suspension; g) clinical investigation report or its summary?		
4.5.5 Continuing information to be obtained from the EC			
	Has the following information been obtained in writing as a minimum from the EC prior to implementation during the clinical investigation:		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	a) approval/favourable opinion of amendments, as stated in 4.5.4 d); b) approval of the request for deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical investigation, as stated in 4.5.4 b); c) approval for resumption of a suspended clinical investigation, as stated in 4.5.4 f), if applicable?		
4.6 Vulnerable populations			
	Have clinical investigations been conducted in vulnerable populations only when they cannot be carried out in non-vulnerable populations and have they followed the additional EC procedures where applicable? Have these clinical investigations been designed specifically to address health problems that occur in the vulnerable population, and offer the possibility of direct health-related benefit to the vulnerable population?		
4.7 Informed consents			
4.7.1 General			
	Has an informed consent been obtained in writing from the subject and has the process been documented before any procedure specific to the clinical investigation is applied to the subject, except when special circumstances described in 4.7.3.4 apply?		
4.7.2 Process of obtaining informed consent			
	Has the general process for obtaining informed consent been documented in the CIP and does it: a) ensure that the principal investigator or his/her authorized designee conducts the informed consent process, b) include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation, c) avoid any coercion or undue improper on, or inducement of, the subject to participate, d) not waive or appear to waive the subject's legal rights, e) use native non-technical language that is understandable to the subject, f) provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation, g) include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process, h) provide the subject with a copy of the signed and dated informed consent form and any other written information,		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	i) show how informed consent will be obtained and recorded in special circumstances (see 4.7.3) where the subject is unable to provide it him- or herself, and j) ensure that important new information is provided to new and existing subjects throughout the clinical investigation?		
4.7.3 Special circumstances for informed consent			
4.7.3.2 Subject needing legally authorized representatives			
	Has informed consent been given by the legally authorized representative only if a subject has been unable to make the decision to participate in a clinical investigation (e.g. infant, child and juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person)? Has the subject, in such cases, been informed about the clinical investigation within his/her ability to understand?		
4.7.3.3 Subject unable to read or write			
	Has informed consent been obtained through a supervised oral process if a subject or legally authorized representative has been unable to read or write? Has an independent witness been presented throughout the process? Have the written informed consent form and any other information been read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, has he personally dated the informed consent form? Has the witness also signed and personally dated the informed consent form attesting that the information was accurately explained and that informed consent was freely given?		
4.7.3.4 Emergency treatments			
4.7.3.4.1	For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, has the informed consent of the subject's legally authorized representative been requested, if present?		
4.7.3.4.2	When it is not possible to obtain prior consent from the subject, and the subject's legally authorized representative is not available, has the subject still been enrolled if a specific process has been described in the CIP as given in A.13 b)?		
4.7.3.4.3	Have arrangements been made to inform the subject or legally authorized representative, as soon as possible, a) about the subject's inclusion in the clinical investigation, and b) about all aspects of the clinical investigation?		
4.7.3.4.4	Has the subject been asked to provide informed consent for continued participation as soon as his/her medical conditions allows?		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
4.7.3.4.5	Has the principal investigator enrolled a subject without obtaining the informed consent of the subject or his/her legally authorized representative only when the following conditions have been fulfilled: c) the prospective subject fulfills the emergency conditions and is obviously in a life-threatening situation; d) no sufficient clinical benefits are anticipated from the current available treatment; e) there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; f) anticipated risks are outweighed by the potential benefits of applying the investigational device; g) the legally authorized representative cannot be promptly reached and informed?		
4.7.4 Information to be provided to the subject			
	Has all information pertinent to the clinical investigator, including at least the following, been provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally authorized representative): a) Description and purpose: 1) statement that the clinical investigation involves research; 2) purpose of the clinical investigation; 3) anticipated duration of the clinical investigation, and extent of the involvement and responsibilities of each subject during the clinical investigation; 4) description of the investigational device and comparator, if any; 5) description of all procedures involving the subject; 6) aspects of the clinical investigation that are experimental; 7) description of the clinical investigation, including a mention of any comparison groups and the method of assignment to each group; 8) number of subjects expected to participate in the clinical investigation? b) Potential benefits: 1) description of benefits for the subject that can reasonably be expected (if there is no direct therapeutic benefit anticipated, this shall be noted); 2) description of potential benefits for others? c) Risks and inconveniences for the subject and, when applicable, for an embryo, foetus, or nursing infant: 1) description of residual risks identified by the risk analysis; 2) description of risks associated with the clinical		

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	procedures required by the CIP; 3) statement that unanticipated risks may occur; 4) description of inconveniences? d) Alternative procedure(s): 1) information on alternative treatments or procedures that may be available to the subject, and their potential benefits and risks? e) Confidentiality: 1) statement confirming that subject participation is confidential; 2) statement confirming that records identifying the subject will be kept confidential to the extent allowed by the law; 3) statement confirming that the subject understands that regulatory authorities, EC representatives and sponsor's representatives involved in the clinical investigation will have direct access to medical records; 4) statement indicating that clinical investigation results may be published without disclosing the subject's identity? f) Compensation: 1) information about provisions for compensation available in the event of injury arising from participation in the clinical investigation; 2) information about additional health care for subjects who suffer from an adverse event as a result of participating in the clinical investigation; 3) information on financial compensation for participation, if applicable? g) Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation? h) Information on the role of sponsor's representative in the clinical investigation? i) Contact persons: 1) whom to contact with questions about the clinical investigation; 2) whom to contact in the event of injury; 3) whom to contact with questions about subject's rights? j) Statement declaring that new finding or the reasons for any amendment to the CIP that affect the subject's continued participation shall be made available to the subject? k) Statement indicating that, upon subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation? l) Termination: 1) circumstances under which the subject's participa-		

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	tion can be terminated by the principal investigator, if applicable; 2) circumstances under which the sponsor can suspend or prematurely terminate the clinical investigation?		
4.7.5 Informed consent signature			
	Does the informed consent signature form contain the following: a) the voluntary agreement to participate in the clinical investigation and follow the investigator's instructions; b) a statement declaring that refusal of participation incurs no penalty for the subject; c) a statement declaring that discontinuation at any time incurs no penalty for the subject; d) a statement with regard to the possible consequences of withdrawal; e) an acknowledgement of the information provided and confirmation that all the subject's questions were answered; f) a statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation; g) a statement confirming that the subject or his/her legally authorized representative agrees that sponsor's representatives, regulatory authorities and EC representatives will be granted direct access to the subject's medical records?		
4.7.6 New information			
	Has new information, that has become available and could have significantly affected a subject's future health and medical care, been provided to the subject(s) affected in written form? If relevant, have all affected subjects been asked to confirm their continuing informed consent in writing?		
5 Clinical investigation planning			
5.1 General			
	Have all parties participating in the conduct of the clinical investigation been qualified by education, training or experience to perform their tasks and has this been documented appropriately (see 8.2.1)?		
5.2 Risk evaluation			

Ref: **Device:** **Date:**

No.	*Quetion*	*Reference / Remark*	*Evaluation*
5.2.1	Have risks, associated with the investigational device, been estimated in accordance with ISO 14971 prior to conducting a clinical investigation? Does the risk analysis include or refer to an objective review of published and available unpublished medical and scientific data? Is a summary of the risk analysis, including an identification of residual risks, included in the IB?		
5.2.2	Does the decision to embark upon a clinical investigation of a medical device require that the residual risk(s), as identified in the risk analysis, as well as risk(s) to the subject associated with the clinical procedure required by the CIP be balanced against the anticipated benefits to the subjects?		
5.2.3	Has the risk analysis been used as a basis for identifying anticipated adverse device effects characterized by their nature, incidence, severity and outcome?		
5.2.4	Have the anticipated adverse device effects been documented in the CIP (see A.4), the IB (see B.5) and the informed consent form (see 4.7.4)?		
5.3 Justification for the design of the clinical investigation			
5.3.1	Is the justification for the design of the clinical investigation based on the evaluation of pre-clinical data and the results of a clinical evaluation?		
5.3.2	Does the clinical evaluation include an assessment and analysis of clinical data concerning safety or performance of the investigational device or similar devices or therapies? Is the evaluation relevant to the intended purpose of the investigational device and the proposed method of use? Is this scientific activity done with rigour and objectivity according to scientific standards using the principles of GHTF clinical evaluation (see Reference [6])?		
5.3.3	Have the results of the clinical evaluation been used to determine and justify the optimal design of the clinical investigation? Have they helped identify relevant endpoints and confounding factors to be taken into consideration, and served to justify the choice of comparator(s)?		
5.3.4	Has the clinical investigation been designed to evaluate whether the investigational device has been suitable for the purpose(s) and the population(s) for which it has been intended? Has it been designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives?		
5.4 Clinical investigation plan (CIP)			
5.4.1	Does the CIP include the information specified in Annex A?		

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No.	*Quetion*	*Reference / Remark*	*Evaluation*
5.4.2	Are the CIP and all subsequent amendments to the CIP agreed upon between the sponsor, the coordinating investigator and all principal investigators, and are they recorded with a justification for each amendment?		
5.5 Investigator's brochure (IB)			
5.5.1	Does the IB provide the principal investigator with sufficient safety or performance data from pre-clinical investigations or clinical investigations to justify human exposure to the investigational device specified in the CIP?		
5.5.2	Has the IB been updated throughout the course of the clinical investigation as significant new information has become available (e.g. a significant change in risk, etc.)?		
5.5.3	Has the principal investigator(s) acknowledged the receipt of the IB and subsequent amendments, and has he kept all information confidential?		
5.5.4	Does the IB include the information specified in Annex B?		
5.6 Case report forms (CRFs)			
5.6.1	Has CRFs been developed to capture the data for each enrolled subject as required by the CIP? Does the CRFs include information on the condition of each subject upon entering, and during the course of, the clinical investigation, exposure to the investigational device and any other therapies (see Annex C)?		
5.6.2	Has a procedure been in place to ensure, that when it has been necessary to amend the CIP, the sponsor has reviewed the CRFs to determine if an amendment of these forms has also been necessary?		
5.7 Monitoring plan			
	Has the sponsor assessed the extent and nature of monitoring appropriate for the clinical investigation, including the strategy for source data verification, based on considerations such as objective, design, complexity, size, critical data points and endpoints of the clinical investigation? Have results of this assessment been used to develop a monitoring plan?		
5.8 Investigation site selection			
	Prior to the initiation of the clinical investigation, have the qualifications of the principal investigator(s) and adequacy of the investigation site(s) been verified and documented in an investigation site selection report? Has the rationale for selecting an investigation site been documented?		
5.9 Agreement(s)			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
5.9.1	Is there an agreement between the sponsor and the principal investigator(s)/investigation site(s) and any other relevant parties (e.g. investigators, CRO(s) and core laboratories), which defines the responsibilities of each party in the clinical investigation?		
5.9.2	Does the agreement indicate that, by participating in a clinical investigation, the parties may share some regulatory responsibilities with the sponsor?		
5.10 Labelling			
	Does the investigational device, the instructions for use or the packaging indicate that the investigational device is exclusively for use in a clinical investigation, if required by national regulations?		
5.11 Data monitoring committee (DMC)			
5.11.1	Has the sponsor considered establishing a DMC prior to starting the clinical investigation?		
5.11.2	Has the decision to establish a DMC been guided by the risk analysis, taking into account both the risks associated with the use of the investigational device and the risks associated with subject's participation in the clinical investigation?		
5.11.3	Has the primary function of the DMC been described in the CIP? Have the responsibilities of the DMC been detailed in the separate written procedures to establish the frequency of meetings, handling of emergency situations and documentation of such meetings?		
6. Clinical Investigation conduct			
6.1 General			
6.1.1	Has the clinical investigation been conducted in accordance with the CIP?		
6.1.2	Has the clinical investigation commenced after written approval/favorable opinion from the EC and, if required, after the relevant regulatory authorities of the countries where the clinical investigation has taken place has been received?		
6.2 Investigation site initiation			
6.2.1	Has an initiation visit for each participating investigation site, or alternatively, an investigator meeting been conducted and documented by the sponsor or monitor at the beginning of the clinical investigation (see 8.2.4)?		
6.2.2	Has a log been initiated identifying names, initials, signatures, functions, and designated authorizations for the principal investigator and members of the investigation site team?		
6.3 Investigation site monitoring			
6.3.1	Has the conduct of the clinical investigation been monitored according to the monitoring plan (see 8.2.4)?		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
6.3.2	In general, has a one-site monitoring been conducted before, during and after the clinical investigation? However, in exceptional circumstances, has the sponsor determined that remote monitoring (without visiting the investigation site), in conjunction with procedures such as investigator's documented training, meetings, and extensive written guidance or telephone communication, could insure appropriate conduct of the clinical investigation? In such circumstances, has the sponsor provided a justification for omitting the source document verification?		
6.4 Adverse events and device deficiencies			
6.4.1 Adverse events			
6.4.1.1	Have all adverse events been documented in a timely manner throughout the clinical investigation and have they been reported as specified in 8.2.5 and 9.8?		
6.4.1.2	Have all adverse events been reported in an interim or final report of the clinical investigation?		
6.4.2 Device deficiencies			
6.4.2.1	Have all devices deficiencies related to the identity, quality, durability, reliability, safety or performance of an investigational medical device been documented throughout the clinical investigation and appropriately managed by the sponsor?		
6.4.2.2	Have device deficiencies that did not lead to an adverse event but could have led to a medical occurrence been: a) If either suitable action had not been taken, b) If intervention had not been made, or c) If circumstances had been less fortunate, reported as specified in 8.2.5 and 9.8?		
6.5 Clinical investigation documents and documentation			
6.5.1 Amendements			
	Have the IB, CIP, CRFs, informed consent from and other subject information, or other clinical investigation documents been amended as needed throughout the clinical investigation, and a justification statement agreed upon between the sponsor and principal investigator, or the coordinating investigator? Have proposed amendments to the CIP been agreed upon between the sponsor and principal investigator, or the coordinating investigator? Have the amendments to the CIP and the subject's informed consent form been notified to, or been approved by, the EC and regulatory authorities, if required (see 4.5.4)? Have the version number and date of amendments been documented?		
6.5.2 Subject Identification log			
	Has each investigation site maintained a log of all the subjects		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	enrolled in the clinical investigation, assigning an identification code lined to their names, alternative subject identification or contact information?		
6.5.3 Source documents			
	Have source documents been created and maintained by the investigation site team throughout the clinical investigation?		
6.6 Additional members of the investigation site team			
	Have new members of the investigation site team been added from time to time at new or existing sites? Has new personal only started their assignment after receiving adequate training in the clinical investigation requirements and has this training been documented? Have names, initials, signatures, functions, and designated authorizations of new personnel been documented?		
6.7 Subject privacy and confidentiality of data			
6.7.1	Has confidentiality of data been observed by all parties involved at all times throughout the clinical investigation? Have all data been secured against unauthorized access?		
6.7.2	Has the privacy of each subject and confidentiality of his/her information been preserved in reports and when publishing any data?		
6.7.3	Has the principal investigator or institution provided direct access to source data during and after the clinical investigation for monitoring, audits, EC review and regulatory authority inspections? Has the principal investigator or institution, as required, obtained permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation?		
6.8 Document and data control			
6.8.1 Traceability of documents and data			
6.8.1.1	Have all documents and data been produced and maintained in a way that assures control and traceability? Has the accuracy of translations, where relevant, been guaranteed and documented? Have all documents and subsequent versions, related to a clinical investigation been identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation?		
6.8.1.2	Has the investigator assured the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports? Where copies of the original source document as well as printouts of original electronic source documents are retained, have these been signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document?		
6.8.1.3	If assignment to a treatment group is a blinded/masked in any way, has it been safeguarded throughout the clinical investigation, including data entry and processing?		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	Have established procedures for decoding blinded/masked clinical investigations been followed?		
6.8.2 Recording of data			
	Have the data reported on the CRFs been derived from source documents and have they been consistent with these source documents, and have any discrepancies been explained in writing? Does the CIP specify which data can be recorded directly in the CRFs? Is the CRFs signed and dated by the principal investigator or his/her authorized designee(s)? Are any changes or correction to data reported on a CRF dated, initialed and explained if necessary, and don't obscure the original entry (i.e. an audit trail shall be maintained); does this apply to both written and electronic changes and corrections?		
6.8.3 Electronic clinical data systems			
	When electronic clinical databases or remote electronic clinical data system are used, have written procedures been implemented to: a) establish and document requirements for the electronic clinical data system to receive and process data, b) verify and validate that the requirements for the electronic clinical data system can be consistently met, c) ensure attributability, completeness, reliability, consistency and logic of the data entered, d) ensure accuracy of reports, e) ensure that data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail), f) maintain a security system that prevents unauthorized access to the data, both internally and externally, g) maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user, h) ensure that all completed CRFs are signed by the principal investigator or authorized designee, i) maintain adequate backup, retention and irretrievability of the data, and j) train users on proper use of the system?		
6.9 Investigational device accountability			
6.9.1	Have investigational devices been controlled and have the investigational devices been used only in the clinical investigation and according to the CIP?		
6.9.2	Has the sponsor kept records to document the physical location of all investigational devices from shipment of investigational devices to the investigational sites until return or dis-		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	posal?		
6.9.3	Has the principal investigator or an authorized designee kept records documenting the receipt, use, return and disposal of the investigational devices, which shall include: a) the date of the receipt, b) identification of each investigational device (batch number/serial number or unique code), c) the expiry date, if applicable, d) the date or dates of use, e) subject identification, f) date on which the investigational device was returned/explanted from subject, if applicable, and g) the date of return of unused, expired or malfunctioning investigational devices, if applicable?		
6.10 Accounting for subjects			
6.10.1	Have all subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) been accounted for and documented?		
6.10.2	If a subject withdraws from the clinical investigation, has the reason been recorded? If such withdrawal is due to problems related to the investigational device safety or performance, has the investigator asked for the subject's permission to follow his/her status/condition outside the clinical investigation?		
6.11 Auditing			
6.11.1	Have audits of the clinical investigation been conducted by the sponsor or third parties designated by the sponsor to evaluate compliance with the CIP, written procedure, this International Standard and the applicable regulatory requirements? Have these audits covered all involved parties, systems and facilities and are independent of, and separate from, routine monitoring or quality control functions?		
6.11.2	Has an audit been useful: a) as a routine part of the sponsor's quality assurance programme, b) to assess the effectiveness of the monitoring activity, c) whenever there are serious or repeated CIP deviations or suspicions of fraud, d) to bring an investigation site into "inspection readiness", i.e. to prepare the investigation site for a potential regulatory inspection, and e) when requested or suggested by a regulatory authority?		
6.11.3	Have the auditors been qualified by training and experience to conduct audits properly?		

Ref: **Device:** **Date:**

No.	*Quetion*	*Reference / Remark*	*Evaluation*
6.11.4	Has the auditing of clinical investigation systems been conducted in accordance with the sponsor's written procedures or specific plan on what to audit, how to audit, the frequency of audits and the form and content of audit reports?		
6.11.5	Have the sponsor's audit plan and procedures for a clinical investigation audit been guided by the importance of the clinical investigation, the level of risk to the subjects and any identified problem(s)?		
6.11.6	Have the audit results been documented and communicated to relevant parties, if applicable?		
7 Suspension, termination and close-out of the clinical investigation			
7.1 Suspension or premature termination of the clinical investigation			
7.1.1 Procedure for suspension or premature termination			
7.1.1.1	Has the sponsor suspended or prematurely terminated either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons?		
7.1.1.2	Has a principal investigator, EC, or regulatory authority suspended or prematurely terminated participation in a clinical investigation at the investigation sites for which they are responsible?		
7.1.1.3	If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when instructed by the EC or regulatory authorities, has the sponsor suspended the clinical investigation while the risk is assessed? Has the sponsor terminated the clinical investigation if an unacceptable risk is confirmed?		
7.1.1.4	Has the sponsor considered terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator?		
7.1.1.5	If suspension or premature termination occurs, has the terminating party justified its decision in writing and promptly informed the other parties with whom they are in direct communication? Have the principal investigator and sponsor kept each other informed of any communication received from either the EC or the regulatory authority?		
7.1.1.6	If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, has the sponsor informed the responsible regulatory authority as appropriate and ensured that the EC is notified, either by the principal investigator or by the sponsor? If the suspension or premature termination was in the interest of safety, has the sponsor informed all other principal investigators?		

Ref: **Device:** **Date:**

No.	*Quetion*	*Reference / Remark*	*Evaluation*
7.1.1.7	If suspension or premature termination has occurred, a) has the sponsor remained responsible for providing resources ti fulfil the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical investigation, and b) has the principal investigator or authorized designee promptly informed the enrolled subjects at his/her investigation site, if appropriate? Have all activities listed in 7.2 also been conducted?		
7.1.2 Procedure for resuming the clinical investigation after temporary suspension			
7.1.2.1	When the sponsor has concluded an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decided to lift the temporary suspension, has the sponsor informed the principal investigators, the ECs, and, where appropriate, the regulatory authorities of the rationale and provided them with the relevant data supporting this decision?		
7.1.2.2	Has concurrence been obtained from the ECs and, where appropriate, regulatory authorities before the clinical investigation resumes?		
7.1.2.3	If subjects have been informed of the suspension, has the principal investigator or authorized designee informed them of the reasons for resumption?		
7.2 Routine close-out			
	Have routine close-out activities been conducted to ensure that the principal investigator's records are complete, all documents needed for the sponsor's files are retrieved, remaining clinical investigation materials are disposed of, previously identified issues have been resolved and all parties are notified? a) Does completing the records include ensuring that 1) all essential documents are complete and up to date, 2) all CRFs are completed, 3) all outstanding queries are resolved, 4) the current status of all ongoing adverse events is documented, 5) arrangements are made for archiving and record retention, and 6) documenting disposition of any: i.) investigational devices; ii.) remaining samples (e.g. blood or tissue); iii.) other clinical investigation materials? b) Does notification include 1) Notification to EC, and 2) Notification to regulatory authorities, if required?		
7.3 Clinical investigation report			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	After close-out the clinical investigation, has a report of the clinical evaluation been completed in accordance with the applicable regulations, even if the clinical investigation was terminated prematurely? a) Is the clinical investigation report in written form? b) Does the clinical investigation report include identification of the device(s), a description of the methodology and design of the clinical investigation, any deviations from the CIP, data analysis together with any statistics and a critical appraisal of the aims of the clinical investigation? c) Does the clinical investigation report take into account the data from each investigation site and for all subjects? Are no subjects identifiable either from the clinical investigation or the published results? d) Where applicable, has the clinical investigation report been made available to the coordinating investigator and all principal investigators for review and comment? Does the sponsor maintain records confirming that the clinical investigation report has been provided for review? If a reviewer does not agree with all or part of the clinical investigation report, has his/her comments been recorded and communicated to the other principal investigators? e) Where required by national regulations, have the sponsor and coordinating investigator been asked to provide their signature, indicating their agreement with the content of the clinical investigation report? If no coordinating investigator has been appointed, has the signature of the principal investigator(s) been obtained? f) In accordance with applicable requirements, has the clinical investigation report been provided to the EC(s) and regulatory authorities?		
7.4 Document retention			
	Have the sponsor and principal investigator maintained the clinical investigation documents as required by the applicable regulatory requirement(s)? Have they taken measures to prevent accidental or premature destruction of these documents? Has the principal investigator or sponsor transferred custody of records to another person/party and document the transfer at the investigation site or at the sponsor's facility?		
8 Responsibility of the sponsor			
8.2 Clinical quality assurance and quality control			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
8.2.1	Have quality assurance and quality control principles applied to the processes of the clinical investigation? Has the sponsor a) implemented and maintained written clinical quality procedures to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, recorded and reported in compliance with this International Standard, the CIP, any subsequent amendment(s), and any other applicable standards and regulatory requirements, b) maintained records to document the compliance of all parties involved in the clinical investigation, c) ensured that the auditing requirements of 6.11 are met, if applicable, and d) justify and document significant exceptions to the requirements of this International Standard?		
8.2.2	Have clinical quality assurance and quality control been integrated in the sponsor's overall quality system?		
8.2 Clinical investigation planning and conduct			
8.2.1 Selection of clinical personnel			
	Has the sponsor, prior to commencement of the clinical investigation: a) defined, established and allocated all the roles and responsibilities related to the clinical investigation in one or more written agreements, as defined in 5.9, b) selected appropriately qualified principal investigators, as outlined in 5.8 and 9.2, c) selected a coordinating investigator, if appropriate, as in the case of a multicenter investigation, d) received disclosures of conflict of interest from principal investigators and investigators, where required by national regulations, e) ensured the members of the investigation site team and are their designated authorization(s) identified in a log with details, as defined in 6.2, f) designated or appointed one or more monitors, or otherwise assumed the responsibilities of the monitor(s), and g) ensured documentation of training, experience and scientific or clinical knowledge for all the relevant parties involved in order to adequately conduct the clinical investigation, including training, on 1) the use of the investigational device(s), 2) device accountability procedures (see 6.9), 3) IB, 4) CIP, 5) CRFs and instructions for completion, 6) the written informed consent form and process as well as other written information provided to sub-		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	jects, and 7) sponsor's written procedures, this International Standard and any applicable regulatory requirements; h) ensured that, in multicentre investigations, all investigators and other parties involved are given instructions on uniformly assessing and documenting clinical and laboratory findings, i) ensured that any clinical-investigation-related activities of sponsor representative(s) at the investigation site(s) are described in the CIP and the informed consent form, and that these activities occur in such a way that they do not bias the data integrity, j) considered the need for a DMC and, if appropriate, establish the committee?		
8.2.2 Preparation of documents and materials			
	Has the sponsor prior to commencement of the clinical investigation a) prepared the documents, as described in Clauses 4,5 and 6, and ensured they are approved by the relevant persons by dated signature; if required, have copies been provided to all parties involved, and dated signatures obtained as appropriate, b) assured the accuracy of the translation, where relevant, c) ensured that a supply of investigational devices, as characterized in 6.9, is available in a timely manner for the clinical investigation; have investigational devices not been made available to the principal investigator until all requirements to start the clinical investigation are met, d) provided insurance covering the cost of treatment of subjects in the event of clinical-investigation-related injuries, in accordance with the national regulations if applicable, e) documented any financial arrangement(s) between the principal investigator or the investigation site and the sponsor, f) submitted any required application(s) to begin the clinical investigation in a given country to the appropriate regulatory authority(ies) for review, acceptance or permission [as per applicable regulatory requirement(s)], g) ensured that EC's approval/favourable opinion is obtained and documented, and that appropriate provisions are made to meet any conditions imposed by the EC, and h) ensured that any modification(s) required by the EC or regulatory authority are made and documented by the principal investigator and have gained the ap-		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	proval/favourable opinion of the EC or regulatory authority?		
8.2.3 Conduct of clinical investigation			
	Has the sponsor been responsible for a) accountability of investigational devices throughout the clinical investigation, b) documenting correspondence with all parties involved in the clinical investigation, including ECs and regulatory authorities, c) ensuring that the clinical investigation is appropriately monitored by determining the extent and nature of monitoring, including the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points and endpoints of the clinical investigation, d) reviewing the monitoring report(s) and following up any action(s) required in the monitoring report(s) (see also 8.2.4.7), e) taking prompt action to secure compliance with all clinical investigation requirements, and f) submitting progress reports, including safety summary and deviations, when requested, to all reviewing ECs and the regulatory authorities?		
8.2.4 Monitoring			
8.2.4.1 General			
	Has the clinical investigation monitoring verified that the conduct of the clinical investigation complies with the approved CIP, subsequent amendment(s), this International Standard, and the applicable regulatory requirement(s)?		
8.2.4.2 Qualifications of the monitor			
8.2.4.2.1	Are monitors: a) qualified in the field of this International Standard through training and experience as well as scientific or clinical knowledge; b) knowledgeable on the use of the investigational device(s) and relevant requirements, CIP and informed consent process (see 4.7); c) trained on the sponsor's clinical quality assurance and quality control system as well as any special procedures for monitoring a specific clinical investigation?		
8.2.4.2.2	Have trainings been documented in the sponsor's files?		
8.2.4.3 Assessment of the investigation site			
	Has the monitor assessed each investigation site to verify that the principal investigator has: a) adequate qualifications; b) adequate resources, including facilities, laboratories, equipment and a qualified investigation site team; c) access to an adequate number of subjects?		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
8.2.4.4 Initiation of the investigation site			
	Has the monitor initiated each investigation site to ensure that the principal investigator and investigation site team a) have received and understood the requirements and contents of 1) CIP, 2) IB, 3) the informed consent form, 4) CRFs, 5) the instructions for use, 6) any written clinical investigation agreements, as appropriate, b) have access to an adequate number of investigational devices c) have been trained in the use of the investigational device, and d) are familiar with the responsibilities of the principal investigator, as described in Clause 9?		
8.2.4.5 Routine on-site monitoring visits			
	Has the monitor performed routine on-site monitoring visits to verify that a) compliance with the CIP, any subsequent amendment(s), this International Standard and regulatory requirements has been maintained; have deviations been discussed with the principal investigator(s) or authorized designee, documented and reported to the sponsor, b) only authorized individuals, as described in 8.2.1 e), have been participating in the clinical investigation, c) the investigational device has been used according to the CIP or instructions for use and that, where modifications have been required to the device, its method of use or the CIP, these have been reported to the sponsor, d) investigation site resources, including laboratories, equipment and the investigation site team, have remained adequate throughout the duration of the clinical investigation, e) the principal investigator continued to have access to an adequate number of subject and investigational devices, f) signed and dated informed consent forms have been obtained from each subject at the point of enrolment or before any clinical-investigation-related procedures have been undertaken, g) source documents and other clinical investigation records have been accurately, complete, up to date, stored and maintained appropriately, h) CRFs and queries are complete, recorded in a timely		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	manner, and consistent with source documents, i) appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialed by the principal investigator or by his/her authorized designee; has the monitor not made corrections, additions or deletions to the CRFs, j) all adverse events and device deficiencies have been reported to the sponsor, and all serious adverse events and device deficiencies that could have led to a serious adverse device effect have been reported to the sponsor without unjustified delay, k) all serious adverse events and deviations have been reported to the EC, if required, l) the storage and investigational accountability are correct and the traceability process has been followed, m) all other required reports, notifications, applications, submissions and correspondence have been maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical investigation, n) maintenance and calibration of the equipment relevant to the assessment of the clinical investigation has been appropriately performed and documented, where applicable, o) current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file, if required, p) subject withdrawal has been documented; has the monitor discussed this with the principal investigator or his/her authorized designee, q) subject non-compliance with the requirements stated in the informed consent has been documented; has the monitor discussed this with the principal investigator or his/her authorized designee, r) the principal investigator and investigation site team have been informed and knowledgeable of all relevant document updates concerning the clinical investigation, and s) any corrective and preventive actions, as needed, have been implemented and are effective?		
8.2.4.6 Close-out activities			
	Has the monitor performed close-out activities as described in Clause 7?		
8.2.4.7 Monitoring reports			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
8.2.4.7.1	Have all monitoring activities been documented in a written report to the sponsor [see also 8.2.3 d)] and do they include a) the date, investigation site identification, name of the monitor and name of the principal investigator or other individuals contacted, and b) a summary of what the monitor reviewed and his/her observation(s) with regard to the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance?		
8.2.4.7.2	Has a copy of the monitoring report or a summary of key findings been shared with the principal investigator in writing?		
8.2.5 Safety evaluation and reporting			
	Is the sponsor responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and has he a) reviewed the investigator's assessment of all adverse events and determined and documented in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), has the sponsor communicated both opinions to concerned parties, as defined in c), d) and e) below, b) reviewed all device deficiencies and determined and documented in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), has the sponsor communicated both opinions to concerned parties, as defined in c), d) and e) below, c) reported or ensured the reporting, to the EC by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP or by the EC, d) reported to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP, e) reported all relevant safety information to the DMC, if established, according to written procedures, f) in the case of a multicentre clinical investigation, informed all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensured that they are reported to their EC, if required by national regulations or the CIP or by the EC, whichever is more stringent; has this information been sent to all the principal investigators within a time frame estab-		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	lished based on the perceived risk as defined in the risk analysis report, g) ensured that the EC and the regulatory authorities are informed of significant new information about the clinical investigation, and h) in case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determined whether the risk analysis needed to be updated and assessed whether corrective or preventive action was required?		
8.2.6 Clinical investigation close-out			
	Has the sponsor a) ensured all clinical investigation close-out activities were properly conducted as described in Clause 7, b) provided a statistical analysis of the data, c) produced a clinical investigation report and submitted it for review, as described in 7.3, and d) ensured that the clinical investigation report, whether for a completed or prematurely terminated clinical investigation, has been provided to the EC, participating investigators and regulatory authorities, as required by national regulations?		
8.3. Outsourcing of duties and functions			
8.3.1	Has the sponsor transferred any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation data has been resided with the sponsor? Have all requirements in this International Standard applying to a sponsor been also applied to the external organization inasmuch as this organization assumes the clinical-investigation-related duties and functions not specifically transferred to, and assumed by, the external organization?		
8.3.2	Has the sponsor specified in writing any clinical-investigation-related duty or function assumed by the external organization, retaining any clinical-investigation-related duties and functions not specifically transferred to, any assumed by, the external organization?		
8.3.3	Has the sponsor been responsible for verifying the existence of and adherence to written procedures at the external organization?		
8.4 Communication with regulatory authorities			
	Has the sponsor, if required a) notified or obtained approval from regulatory authorities in the country where the clinical investigation was conducted, b) reported on the progress and status of the clinical investigation, and c) performed safety reporting as specified in 8.2.5?		

Ref: **Device:** **Date:**

No.	*Quetion*	*Reference / Remark*	*Evaluation*
9 Responsibilities of the principal investigator			
9.1 General			
9.1.1	Has the principal investigator implemented and managed the day-to-day conduct of the clinical investigation as well as ensured data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation?		
9.2.2	If the sponsor has contracted an institution to conduct the clinical investigation, has the institution appointed an appropriately qualified person to be the principal investigator?		
9.2 Qualification of the principal investigator			
	Has the principal investigator a) been qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; have evidence of such qualifications of the principal investigator and key members of the investigation site team been provided to the sponsor through up-to-date CVs or other relevant documentation, b) been experienced in the field of application and training in the use of the investigational device under consideration, c) disclosed potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and d) been knowledgeable with the method of obtaining informed consent?		
9.3 Qualification of investigation site			
	Has the principal investigator been able to demonstrate that the proposed investigation site a) has the required number of eligible subjects needed within the agreed recruitment period, and b) has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation?		
9.4 Communication with the EC			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
9.4.1	Has the principal investigator a) provided the sponsor with copies of any clinical-investigation-related communications between the principal investigator and the EC, b) complied with the requirements described in 4.5, c) obtained the written and dated approval/favourable opinion of the EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required, d) performed safety reporting as specified in 9.8, and e) promptly reported any deviations from the CIP that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the EC, CIP or national regulations?		
9.4.2	Has the communication with the EC in particular circumstances been performed by the sponsor, partly or in full, has the sponsor, in this case kept the principal investigator informed?		
9.5 Informed consent process			
	Has the principal investigator a) complied with the requirements specified in 4.7, b) ensured compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and c) ensured and documented appropriate training in an authorized designee has been appointed to conduct the informed consent process?		
9.6 Compliance with CIP			
	Has the principal investigator a) indicated his/her acceptance of the CIP in writing, b) conducted the clinical investigation in compliance with the CIP, c) created and maintained source documents throughout the clinical investigation and made them available as requested during monitoring visits or audits, d) ensured that the investigational device has been used solely by authorized users as specified in 6.2, and in accordance with the CIP and instructions for use, e) proposed to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device, f) refrained from implementing any modifications to the CIP without agreement from the sponsor, EC and the regulatory authorities, if required, g) documented and explained any deviation from the approved CIP that occurred during the course of the clinical investigation, h) ensured that an adequate investigation site team and		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	facilities exist and are maintained and documented during the clinical investigation, i) ensured that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation has been appropriately performed and documented, where applicable, j) ensured the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports, k) maintained the device accountability records, l) allowed and supported the sponsor to perform monitoring and auditing activities, m) been accessible to the monitor and responded to questions during monitoring visits, n) allowed and supported regulatory authorities and the EC when performing auditing activities, o) ensured that all clinical-investigation-related records are retained as specified in 7.4, and p) signed the clinical investigation report, as specified in 7.3?		
9.7 Medical care of subjects			
	Has the principal investigator a) provided adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events, as described in the informed consent [see 4.7.4 f)], b) informed the subject of the nature and possible cause of any adverse events experienced, c) provided the subject with the necessary instructions on proper use, handling, storage and return of the investigational device, when it has been used or operated by the subject, d) informed the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required, e) provided the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and made the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed, f) ensured that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation, g) if appropriate, have subjects enrolled in the clinical investigation been provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (have contact address and telephone numbers been provided?), h) informed, with the subject's approval or when required		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and i) made all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights?		
9.8 Safety reporting			
	Has the principal investigator a) recorded every adverse event and observed device deficiency, together with an assessment, b) reported to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; has this information been promptly followed by detailed written reports, as specified in the CIP, c) reported to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effects, if required by the national regulations or CIP or by the EC, d) reported to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and e) supplied the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event?		
Annex A Clinical investigation plan (CIP)			
A.1 General			
A.1.1 Introduction			
	Have the content of the CIP and any subsequent amendments included all the topics listed in this annex, together with a justification for each topic if this is not self-explanatory?		
A.1.2 Identification of the clinical investigation plan			
	a) Title of the clinical investigation? b) Reference number identifying the specific clinical investigation, if any? c) Version or date of the CIP? d) Summary of the revision history in the case of amendments? e) Version/issue number and reference number, if any, with the page number and the total number of pages on each page of the CIP?		
A.1.3 Sponsor			
	Does the CIP contain the name and address of the sponsor of the clinical investigation?		
A.1.4 Principal investigator, coordinating investigator and investigation site(s)			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
A.1.4.1	a) Name, address, and professional position of 1) principal investigator(s), 2) coordinating investigator, if appointed? b) Name and address of the investigation site(s) in which the clinical investigation would have been conducted? c) Name(s) and address(es) of other institutions involved in the clinical investigation?		
A.1.4.2	Has the sponsor maintained an updated list of principal investigators, investigation sites, and institutions? Has the definitive list been provided with the clinical investigation report (see Annex D)?		
A.1.5 Overall synopsis of the clinical investigation			
	Does the summary or overview of the clinical investigation include all the relevant information regarding the clinical investigation design such as inclusion/exclusion criteria, number of subjects, duration of the clinical investigation, follow-up, objective(s) and endpoint(s)?		
A.2 Identification and description of the investigational device			
	Has the following information been included a) Summary description of the investigational device and its intended purpose? b) Details concerning the manufacturer of the investigational device? c) Name or number of the model/type, including software version and accessories, if any, to permit full identification? d) Description as to how traceability should have been achieved during and after the clinical investigation, for example by assignment of lot numbers, batch numbers or serial numbers? e) Intended purpose of the investigational device in the proposed clinical investigation? f) The populations and indications for which the investigational device is intended? g) Description of the investigational device including any materials that has been in contact with tissues or body fluids? (Does this include details of any medicinal products, human or animal tissues or their derivatives, or other biologically active substances?)? h) Summary of the necessary training and experience needed to use the investigational device? i) Description of the specific medical or surgical procedures involved in the use of the investigational device?		
A.3 Justification for the design of the clinical investigation			
	Is justification for the design of the clinical investigation, based on the conclusions of the evaluation, as specified in 5.3, and does it comprise a) An evaluation of the results of the relevant pre-clinical testing/assessment carried out to justify the use of the		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	investigational device in human subjects, and b) an evaluation of clinical data that are relevant to the proposed clinical investigation?		
A.4 Risks and benefits of the investigational device and clinical investigation			
	Does the CIP include a) Anticipated clinical benefits? b) Anticipated adverse device effects? c) Residual risks associated with the investigational device, as identified in the risk analysis report? d) Risks associated with participation in the clinical investigation? e) Possible interactions with concomitant medical treatment? f) Steps that will be taken to control or mitigate the risks?		
A.5 Objectives and hypotheses of clinical investigation			
	a) Objectives, primary and secondary? b) Hypotheses, primary and secondary, to be accepted or rejected by statistical data from the clinical investigation? c) Claims and intended performance of the investigational device that are to be verified? d) Risks and anticipated adverse device effects that are to be assessed?		
A.6 Design of the clinical investigation			
A.6.1 General			
	a) Description of the type of clinical investigation to be performed (e.g. comparative double-blind, parallel design, with or without a comparator group) with rationale for the choice? b) Description of the measures to be taken to minimize or avoid bias, including randomization and blinding/masking? c) Primary and secondary endpoints, with rationale for their selection and measurement? d) Methods and timing for assessing, recording, and analyzing variables? e) Equipment to be used for assessing the clinical investigation variables and arrangements for monitoring maintenance and calibration? f) Any procedures for the replacement of subjects?		
A.6.2 Investigational device(s) and comparator(s)			
	a) Description of the exposure to the investigational device(s) or comparator(s), if used? b) Justification of the choice of comparator(s)? c) List of any other medical device or medication to be used during the clinical investigation? d) Number of investigational devices to be used, together		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	with a justification?		
A.6.3 Subjects			
	Does the CIP include the following information about the subjects: a) Inclusion criteria for subject selection? b) Exclusion criteria for subject selection? c) Criteria and procedures for subject withdrawal or discontinuation? d) Point of enrolment? e) Total expected duration of the clinical investigation? f) Expected duration of each subject's participation? g) Number of subjects required to be included in the clinical investigation? h) Estimated time needed to select this number (i.e. enrolment period)?		
A.6.4 Procedures			
A.6.4.1	Does the CIP contain: a) Description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation? b) Description of those activities performed by sponsor representatives (excluding monitoring)? c) Any known or foreseeable factors that may compromise the outcome of the clinical investigation or interpretation of results?		
A.6.4.2	Does the follow-up period during the clinical investigation permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the investigational device and allow any risks associated with adverse device effects over that period to be identified and assessed?		
A.6.4.3	Does the CIP specifically address what medical care, if any, would have been provided for the subjects after the clinical investigation has been completed?		
A.6.5 Monitoring plan			
	Does the CIP contain general outline of the monitoring plan to be followed, including access to source data and the extend of source data verification?		
A.7 Statistical considerations			
	With reference ti A.5 and A.6, does the CIP contain the description of any justification for: a) statistical design, method and analytical procedures, b) sample size, c) the level of significance and the power of the clinical investigation, d) expected drop-out rates, e) pass/fail criteria to be applied to the results of the clinical investigation, f) the provision for an interim analysis, where applicable,		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	g) criteria for the termination of the clinical investigation on statistical grounds, h) procedures for reporting any deviation(s) from the original plan, i) the specification of subgroups for analysis, j) procedures that take into account all the data, k) the treatment of missing, unused or spurious data, including drop-outs and withdrawals, l) the exclusion of particular information from the testing of the hypothesis, if relevant, and m) in multicenter clinical investigations, the minimum and maximum number of subjects to be included for each center? Do special reasoning and sample size(s) apply for the early clinical investigation(s), e.g. feasibility clinical investigation(s)?		
A.8 Data management			
	Does the CIP contain: a) Procedures used for data review, database cleaning, and issuing and resolving data queries? b) Procedures for verification, validation and securing of electronic data systems, if applicable? c) Procedures for data retention? d) Specified retention period? e) Other aspects of clinical quality assurance, as appropriate?		
A.9 Amendments to the CIP			
	Does the CIP contain descriptions of the procedures to amend the CIP?		
A.10 Deviations from clinical investigation plan			
	a) Statement specifying that the investigator is not allowed to deviate from the CIP, except as specified in 4.5.4 b)? b) Procedures for recording, reporting and analyzing CIP deviations? c) Notification requirements and time frames? d) Corrective and preventive actions and principal investigator disqualification criteria?		
A.11 Device accountability			
	Does the CIP contain a description of the procedures for the accountability of investigational devices as specified in 6.9?		
A.12 Statements of compliance			
	Does the CIP contain: a) Statement specifying that the clinical investigation shall be concluded in accordance with the ethical principles that have their origin in the Declaration of Helsinki (see Reference [8])? b) Statement specifying compliance with this International Standard and any regional or national regulations, as appropriate?		

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	c) Statement specifying that the clinical investigation shall not begin until the required approval/favourable opinion from the EC or regulatory authority have obtained, if applicable? d) Statement specifying that any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate? e) Statement specifying the type of insurance that shall be provided for subjects, if appropriate?		
A.13 Informed consent process			
	Does the CIP contain: a) Description of the general process for obtaining informed consent, including the process for providing subjects with new information, as needed? b) Description of the informed consent process in circumstances where the subject is unable to give it; in the case of emergency treatment, are the items specified in 4.7.3.4 included?		
A.14 Adverse events, adverse device effects and device deficiencies			
	Does the CIP contain the following information: a) Definitions of adverse events and adverse device effects? b) Definition of device deficiencies? c) Definitions of serious adverse events and serious adverse device effects and, where appropriate, unanticipated serious adverse device effects? d) Time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority? e) Details of the process for reporting adverse events (date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the investigational device)? f) Details of the process for reporting device deficiencies? g) List of foreseeable adverse events and anticipated adverse devices effects, together with their likely incidence, mitigation or treatment? h) Emergency contact details for reporting serious adverse events and serious adverse device effects? i) Information regarding the DMC, if established?		
A.15 Vulnerable population			
	Does the CIP contain: a) Description of the vulnerable population? b) Description of the specific informed consent process? c) Description of the EC's specific responsibility? d) Description of what medical care, if any, will be provided for subjects after the clinical investigation has been completed?		
A.16 Suspension or premature termination of the clinical investigation			

Ref: **Device:** **Date:**

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	Does the CIP contain the following information: a) Criteria and arrangements for suspention or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites? b) Criteria for access to and breaking the blinding/masking code in the case of suspension or premature termination of the clinical investigation, if the clinical investigation involves a blinding/masking technique? c) Requirements for subject follow-up?		
A.17 Publication policy			
	Does the CIP contain: a) Statement indicating whether the results of the clinical investigation will be submitted for publication? b) Statement indicating the conditions under which the results of the clinical investigation will be offered for publication?		
A.18 Bibliography			
	Does the CIP contain a list of bibliographic references pertaining to clinical investigation?		
Annex B Investigator's brochure (IB)			
B.1 General			
B.1.1 Introduction			
B.1.1.1	If the required information of the IB is provided in other documentation (e.g. the CIP or instructions for use), are such documents referenced in the IB and made available upon request?		
B.1.1.2	Does the content of the IB contain, as a minimum, all topics listed in this annex?		
B.1.2 Identification of the IB			
	Does the identification of the IB contain: a) Name of the investigational device? b) Documents reference number, if any? c) Version or date of the IB? d) Confidentiality statement, if appropriate? e) Summary of the revision history in the case of amendments, if appropriate? f) A version/issue number and reference number, if any, with the page number and the total number of pages on each page of the IB?		
B.1.3 Sponsor/manufacturer			
	Name and address of the sponsor or manufacturer of the investigational device?		
B.2 Investigational device information			

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	a) Summary of the literature and evaluation supporting the rationale for the design and intended use of the investigational device? b) Statement concerning the regulatory classification of the investigational device, if relevant? c) General description of the investigational device and its components including materials used? d) Summary of relevant manufacturing processes and related validation processes? e) Description of the mechanism of action of the investigational device, along with supporting scientific literature? f) Manufacturer's instructions for installation and use of the investigational device, including any necessary storage and handling requirements, preparation for use and any intended re-use (e.g. sterilization), any pre-use safety or performance checks and any precautions to be taken after use (e.g. disposal), if relevant? g) Description of the intended clinical performance?		
B.3 Preclinical testing			
B.3.1	Is there a summary of the preclinical testing that has been performed on the investigational device, together with an evaluation of the results of such testing justifying its use in human subjects?		
B.3.2	Does the summary include, or where applicable, reefr to the results of: a) design calculations, b) in vitro tests, c) mechanical and electrical tests, d) reliability tests, e) validation of software relating to the function of the device, f) any performance tests, g) ex vivo tests, and h) an evaluation of biological safety?		
B.4 Existing clinical data			
	a) Summary of relevant previous clinical experience with the investigational device and with medical devices that have similar characteristics, including such characteristics that relate to other indications for use of the investigational device? b) Analysis of adverse device effects and any history of modification or recall?		
B.5 Risk management			
	a) Summary of risk analysis, including identification of residual risks? b) Result of the risk assessment? c) Anticipated risks, contra-indications, warnings, etc. for the investigational device?		
B.6 Regulatory and other references			

Ref: **Device:** **Date:**

No.	*Quetion*	*Reference / Remark*	*Evaluation*
	a) List of International Standards, if any, complied with in full or in part? b) Statement of conformity with national regulations, where appropriate? c) List of references, if relevant?		

Kommentar Auditor/Gutachter/Experte:

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Ref:	Device:	Date:

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