Central Administration of Biological and Innovative products and clinical studies
General Administration of clinical trials

Guideline for Preclinical testing and Clinical Investigation for Medical devices

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1. Introduction

Medical devices are health care products distinguished from drugs for regulatory purposes in most countries based on mechanism of action. Unlike drugs, medical devices operate via physical or mechanical means and are not dependent on metabolism to accomplish their primary intended effect.

Medical device is defined as:

Any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- investigation, replacement, modification, or support of the anatomy, or of a physiological process,
- supporting or sustaining life,
- control of conception,
- cleaning, disinfection or sterilization of medical devices,
- providing information by means of in vitro examination of specimens derived from the human body;
- and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

Conformity Assessment of the Investigational Medical Device:

Conformity assessment is the systematic and ongoing examination of evidence and procedures to ensure that a medical device complies with the Essential Principles. Conformity assessment provides objective evidence of the safety, performance, benefits and risk. It is a way by which medical devices manufacturers demonstrates to EDA that its medical device complies with local regulation and EDA guidelines.

Conformity assessment involves the followings:

- Technical documentation for the design of the devices
- Manufacturing processes used to make the devices
- Risk analysis
- Clinical evidence
- Ongoing monitoring and vigilance procedures that will be in place once the device is available for supply

2. Scope:

This document is intended to provide guidance to those involved in designing preclinical and clinical studies intended to support clinical development for medical devices. This guidance frames EDA recommendations in terms of two broad categories of medical devices:

• Therapeutic e.g. Continuous Positive Airway Pressure (CPAP) Machine and aesthetic devices e.g. (Intense Pulsed Light (IPL) Devices)

• Diagnostic devices e.g. Glucose Monitoring System for Diabetes Management

This guidance is directed to manufacturers, stakeholders or any other interested parties. The purpose of this document is to act as guidance for preclinical testing and clinical investigation requirements for one of the following cases of medical devices:

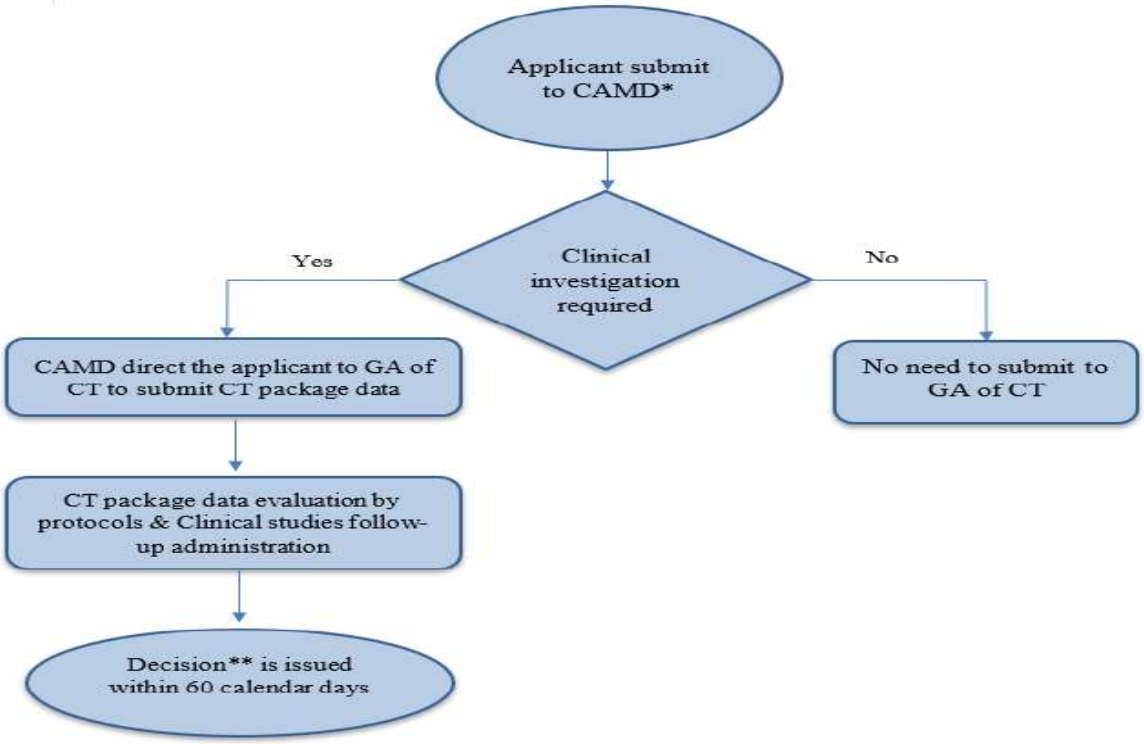
1) Locally manufactured medical devices
2) Imported Medical devices with no granted international quality certification (e.g.: CE mark in EU MDR, 5(10)K or PMA in FDA)
3) Medical devices already on the market (either with international quality certification or not) that are being evaluated for new intended uses, new populations, new materials or design changes.
4) Any other cases that require preclinical and clinical testing for medical devices and IVDs as per EDA regulations and NRA opinion/ requirements.

This guidance also includes principles that are applicable to the device-specific issues such as combination products (in other terms called device containing ancillary products such as drugs, biologicals, etc….) and software as a medical device SaMD. This guideline should be read in conjunction with Clinical Trials Law 214/2020 and its executive regulation (No. 927/ 2022) and relevant ISO standards (e.g. ISO 10993, ISO 14155-2020, ISO14971-2019…...etc.) and other relevant guidelines. This guidance is intended to complement other existing guidance of clinical trials oversight *issued by EDA (Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority, EDREX.GL.Bioinn.006) and is* not intended to replace the policies described in other guidance documents. In cases where questions arise, consult the Administration of scientific committees and technical support via ct.scts@edaegypt.gov.eg.

Note:

Figure (1) is illustrating the process of submission of CT package data in case of locally manufactured IMD & devices without international quality certification &/or used in clinical medical research. In case of pathway for submitting CT package data of imported investigational medical devices with international quality certification, Applicant shall refer to Annex III in *"Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority".*

Figure (1) Flow chart for submission pathway for locally manufactured IMD & devices without international quality certification &/or used in clinical medical research



(*) Central Administration of Medical Devices
(**) EDA regulatory decision of CT authorization e.g. protocol approval/ conditional approval/ refusal.

The guideline will provide comprehensive overview for six main sections related to investigational medical devices, as a part of the conformity assessment process:

1) Medical devices classification
2) Requirements for preclinical investigations and animal studies in medical devices
3) Requirements for clinical investigations in medical devices
4) Ethical considerations for clinical studies in medical devices
5) Safety reporting in clinical investigations of medical devices
6) Risk Management for medical devices

3. Abbreviations:

- ADE: Adverse device effect
- ASADE: Anticipated serious adverse device effect
- BEP: Biological Evaluation Plan
- BER: Biological Evaluation Report
- CAB: Conformity Assessment Body
- CAMD: Central Administration of Medical Devices
- CIP: Clinical investigation plan
- CPAP: Continuous Positive Airway Pressure Machine
- CE mark: European Conformity
- DD: Device deficiency
- DMC: Data Monitoring Committee
- EDA: Egyptian Drug Authority
- FSCA: Field Safety Corrective Action
- FSN: Field Safety Notice
- EC: Ethics committee
- GLP: Good Laboratory Practice
- IMD: Investigational Medical Device
- ISO: International Organization for Standardization
- IVDs: In Vitro Diagnostic
- IPL: Intense Pulsed Light Devices
- IB: Investigational brochure
- LOAEL: Lowest Observed Effect Level
- MDSD: Medical Device Safety Department
- NOAEL: No Observed Effect Level
- NCAs: National competent authorities
- OECD: Organization for Economic Co-operation and development
- PMOA: primary mode of action
- PMCF: post-market clinical follow up
- RR: Residual Risk
- SaMD: Software as a Medical Device
- SADE: Serious adverse device effect
- USADE: Unanticipated serious adverse device effect

4. Terms and definitions:

Accessory to a medical device: means an article intended specifically by its manufacturer to be used together with a particular medical device to enable or assist that device to be used in accordance with its intended use.

Active therapeutic device: Any active medical device, whether used alone or in combination with other medical devices, to support, modify, replace or restore biological functions or structures with a view to treatment or alleviation of an illness or injury.

Adverse Event: Any untoward medical occurrence in patients/subjects, users or other persons, whether or not related to the investigational device, that occurred in the course of the investigation. (**Note:** For users or other persons, this definition is restricted to events related to investigational medical devices.)

Adverse device effect (ADE): Any adverse event related to the use of an investigational medical device or a comparator.

NOTE: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Anticipated serious adverse device effect (ASADE): Any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the last risk assessment document upon serious adverse device effect occurred.

Aesthetic devices: Any instrument, apparatus, appliance, implant, material or other article, intended by the manufacturer to be used, alone or in combination, for human beings to provide a desired change in visual appearance, without therapeutic or reconstructive purpose, by its total introduction into the human body, by placing it in contact with the surface of the eye or by inducing cell or tissue modifications, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

Biocompatibility: the ability of a device material to perform with an appropriate host response in a specific situation.

Body orifice: Any natural opening in the body, as well as the external surface of the eyeball, or any permanent artificial opening, such as a stoma or permanent tracheotomy.

Bioresorbable medical device: medical device intended for degradation and resorption in the biological environment of the body.

Biological Evaluation Report: A comprehensive report that summarizes the findings of all the tests conducted, including conclusions and recommendations

Clinical Evidence: The clinical data and its clinical evaluation pertaining to a medical device.

Clinical Investigation: Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance, and/or effectiveness of a medical device.

**Explanation:* This term is synonymous with ‘clinical trial’ and ‘clinical study’.

Clinical investigations include feasibility studies and those conducted for the purpose of gaining market authorization, as well as investigations conducted following marketing approval.

Clinical Investigation Plan: Document that states the rationale, objectives, design and pre-specified analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Clinical Performance: The ability of a medical device to achieve its intended clinical purpose as claimed by the manufacturer.

Conformity Assessment: The systematic examination of evidence generated and procedures undertaken by the manufacturer, under requirements established by the Regulatory Authority, to determine that a medical device is safe and performs as intended by the manufacturer and, therefore, conforms to the Essential Principles of safety & performance of medical devices.

Conformity Assessment Body (CAB): A body, other than a Regulatory Authority, engaged in determining whether the relevant requirements in technical regulations or standards are fulfilled. (In the EU Member States, it is called notified body).

Central circulatory system: The major internal blood vessels including the following: pulmonary veins, pulmonary arteries, cardiac veins, coronary arteries, carotid arteries (common, internal and external), cerebral arteries, brachiocephalic artery, aorta (including all segments of the aorta), inferior and superior vena cava and common iliac arteries.

Causality assessment: The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

CE mark: is a symbol that indicates a product conforms to the essential requirements (related to safety, performance, and quality) of relevant European Union directives and regulations. In the context of medical devices.

Device deficiency (DD): Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Effectiveness: The ability of a medical device to achieve clinically meaningful outcome(s) in its intended use as claimed by the manufacturer.

Endpoint: An indicator used for providing the evidence for safety, clinical performance, and/or effectiveness in a clinical investigation

Ethics committee (EC): Independent body whose responsibility is to review clinical investigations in order to protect the rights, safety, and well-being of human subjects participating in a clinical investigation.

Essential Principles: Fundamental requirements established by regulatory authorities to ensure the safety and performance of medical devices. These principles outline the essential criteria that medical devices must meet to be considered safe, effective, and suitable for their intended use. They serve as a foundation for regulatory compliance and are integrated into conformity assessment processes to verify that medical devices meet the necessary standards.

Field Safety Corrective Action (FSCA): An action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. such actions should be notified via a field safety notice.

Field Safety Notice (FSN): A communication to customers and/or users sent out by a manufacturer or its representative in relation to a Field Safety Corrective Action.
Harm*:* injury or damage to the health of people, or damage to property or the environment
Hazard*:* potential source of harm
Hazardous situation: circumstance in which people, property or the environment is/are exposed to one or more hazards.
In Vitro Diagnostic (IVD) Medical Device: means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.
Note: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.
Informed consent: process by which an individual voluntarily confirms willingness to participate in a particular clinical investigation, after having been informed of all aspects of the investigation that are relevant to the decision to participate.
Incident: Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.
Intended Use / Purpose: The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.
Investigational medical device: medical device being assessed for clinical performance, effectiveness, or safety in a clinical investigation.
NOTE 1: This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.
Legally designated representative: Individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical investigation
leachable substance: chemical removed from a device or material by the action of water or other liquids related to the use of the device.
Lifetime Studies: Expected lifetime and expected service life as the time-period specified by the manufacturer during which the medical device or accessory remains safe and effective for use.
Malfunction: failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.
Objective: main purpose for conducting the clinical investigation.
Residual risk: risk remaining after risk control measures has been implemented.
Risk: combination of the probability of occurrence of harm and the severity of that harm

Risk analysis: systematic use of available information to identify hazards and to estimate the risk

Risk assessment: overall process comprising a risk analysis and a risk evaluation

Risk control: process in which risks are reduced to, or maintained within, specified levels by decisions made and measures implemented.

Risk estimation: process used to assign values to the probability of occurrence of harm and the severity of that harm.

Risk evaluation: process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

Risk management: systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring risk

Safety: freedom from unacceptable risk

Severity: measure of the possible consequences of a hazard

Surgically invasive device:

(a) An invasive device which penetrates inside the body through the surface of the body, with the aid or in the context of a surgical operation.

(b) A medical device which produces penetration other than through a body orifice.

Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device.

Specimen Receptacle: apparatus specifically intended by a manufacturer to obtain, contain and preserve a body fluid or tissue for in vitro diagnostic examination

NOTE 1: Includes devices intended to store a primary sample prior to examination.

NOTE 2: Includes both vacuum and non-vacuum primary sample collection devices.

Serious adverse device effect (SADE):

Any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

Serious incident: Any incident that directly or indirectly led, might have led or might lead to any of the following:

a) The death of a patient, user or other person,

b) The temporary or permanent serious deterioration of a patient's, user's or other person's state of health,

c) A serious public health threat.

Serious Health Threat: Any event type, which results in imminent risk to the study population of death, serious injury, or serious illness that requires prompt remedial action.

Transmissible Agent: an agent capable of being transmitted to a person, as a communicable, infectious or contagious disease.

Transgenic animal model: an animal which is altered by the introduction of recombinant DNA through human intervention. Transgene refers to a segment of recombinant DNA which is either: 1) introduced into somatic cells, or 2) integrated stably into the germline of its animal host strain, and is transmissible to subsequent generations.

The date of awareness: Refers to the first date on which any employee of the Sponsor, authorized representative or Contract Research Organization for the investigation becomes aware of a serious adverse event.

Unanticipated serious adverse device effect (USADE): Any serious adverse device effect, the nature, severity or outcome of which is not consistent with the reference safety information. A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: (added for the purpose of this document) This includes unanticipated procedure-related serious adverse events; that are, serious adverse events occurring during the study procedure that are unrelated to any malfunction or misuse of the investigational medical device.

Use error: user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user

Note 1: Use error includes the inability of the user to complete a task.

Note 2: Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment.

Note 3: Users might be aware or unaware that a use error has occurred.

Note 4: An unexpected physiological response of the patient is not by itself considered use error.

Note 5: A medical device malfunction that causes an unexpected result is not considered a use error.

NOTE 6: Use error includes slips, lapses, and mistakes.

NOTE 7: An unexpected physiological response of the subject does not in itself constitute a use error.

Validation: confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled

Vital physiological process: Means a process that is necessary to sustain life, the indicators of which may include any one or more of the following:

- Respiration;
- Heart rate;
- Cerebral function;
- Blood gases;
- Blood pressure;
- Body temperature.

Vulnerable subjects

individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

5. Medical devices classification

5.1 Structure of the Classification Rules:

The determination of class should be based on rules derived from the potential of a medical device to cause harm to a patient or user (i.e. the hazard it presents) and thereby on its intended use and the technology/ies it utilizes.

The device class is determined according to the following criteria:

1. Risk of device (the potential hazards of using the device or the device falling)
2. The duration of contact with the patient (no contact, transient, short term, long term, implantable)
3. The degree of invasiveness (non-invasive, indirectly invasive, invasive with respect to body orifices, surgically invasive)
4. The part of the body affected by the use of the device (skin, heart, blood, teeth, spinal)
5. Intended purpose (diagnosis, therapeutic, monitoring)

The manufacturer should document its justification for placing its product into a particular class, including the resolution of any matters of interpretation where he has asked EDA for classification rule.

If, based on the manufacturer's intended use, two or more classification rules apply to the device, the device is allocated the highest level of classification indicated.

5.2 Classification of medical devices according to different regulatory systems:

IMDRF Classification System for Medical Devices

CLASS	LEVEL	DEVICE EXAMPLES
A	Low Hazard	Bandages / tongue depressors
B	Low-moderate Hazard	Hypodermic Needles / suction equipment
C	Moderate-high Hazard	Lung ventilator / bone fixation plate
D	High Hazard	Heart valves / implantable defibrillator

EU MDR and EDA Classification System for Medical Devices

CLASS	LEVEL	DEVICE EXAMPLES
I ➢ Class I non sterile ➢ Class I sterile	Lowest risk	- Wound dressing & stethoscope - Colostomy bags– surgical gowns
IIa	Low- medium risk	- Oxygen mask, hearing-aids, blood transfusion tubes, and catheters

IIb	medium -to high risk	- ventilators and intensive care monitoring equipment
III & Implantable	Highest risk	- Absorbable Sutures, Central Venous Catheter, balloon catheters, Joint Replacement, pacemakers, etc.

6. Types of Scientific Evidence

Medical devices can be evaluated using clinical and non-clinical testing methods.
Clinical testing methods for medical devices can include, when appropriate, randomized clinical trials in the appropriate target population, well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well- documented case histories conducted by qualified experts, reports of significant human experience, and testing on clinically derived human specimens (DNA, tissue, organ and cadaver studies).
Non-clinical testing methods can encompass an array of methods including performance testing for product safety/reliability/characterization, human factors and usability engineering testing under simulated conditions of use, animal and cell-based studies, and computer simulations. These tests characterize mechanical, electrical and chemical properties of the devices including but not limited to wear, tensile strength, compression, flow rate, burst pressure, biocompatibility, toxicity, electromagnetic compatibility (EMC), sterility, stability/shelf life data, software validation, and testing of synthetic samples, including cell lines. The information obtained from any clinical and/or non-clinical testing is taken into account during the premarket review process and EDA's benefit-risk determination
Although a great deal of emphasis is placed on the importance of clinical data in demonstrating the safety and effectiveness of a medical device, non-clinical data also can be critical to understanding a device's safety and effectiveness. Medical devices often have attributes that cannot be tested using clinical methods alone and that play a major role in the safety or effectiveness of the device.
Both clinical and non-clinical testing methods may be used to assess the probability or severity of a given risk, and/or the success of risk mitigation.

7. Requirements for non-clinical investigations and animal studies in medical devices

7.1Biological evaluation of medical devices

Biological evaluation of medical devices is performed to determine the acceptability of any potential adverse biological response resulting from contact of the component materials of the device with the body. The device materials should not, either directly (e.g., via surface-bound chemicals or physical properties) or through the release of their material constituents: (i) produce adverse local or systemic effects; (ii) be carcinogenic; or (iii) produce adverse reproductive and/or developmental effects, unless it can be determined that the benefits of the

use of that material outweigh the risks associated with an adverse biological response. Therefore, evaluation of any new device intended for human use warrants information from a systematic analysis to ensure that the benefits provided by the device in its final finished form will outweigh any potential risks produced by device materials over the intended duration and use of the device in or on the exposed tissues.

7.2 What is Biocompatibility?

According to ISO 10993-1:2018, biocompatibility is defined as the ability of a medical device or material to perform with an appropriate host response in a specific application. More specifically, it is the ability of medical device materials to perform its intended function, without producing any undesirable effects in the patient, in terms of tissue response given the specific situation.

As an integral part of biological risk assessment, biocompatibility testing assesses the compatibility of medical devices with a biological system. It includes studies that document the interaction between the device and the various types of living tissues and cells exposed to the device when it comes into contact with patients. Contact time can be classified as: Limited (≤24 hour), prolonged (>24 hours to 30 days), and long term (>30 days) durations of contact.

Biocompatibility testing is a critical aspect of medical device development, ensuring that devices are safe for use within the human body and do not cause adverse reactions. It is a crucial step for any device that comes into direct or indirect contact with the body. Biocompatibility testing involves a series of tests to assess various aspects of biological safety, such as cytotoxicity, sensitization, irritation, systemic toxicity, genotoxicity, and implantation testing, among others. The specific tests required depend on the type of device and its intended use. Biocompatibility testing requirements are evaluated through biological evaluation plan (BEP), which involves determining the potential risks associated with the device, identifying relevant tests, and establishing a testing strategy. The BEP includes many items like:

- **Biological Testing:**
  - Cytotoxicity Testing: Assesses the potential toxicity of the device's materials to cells.
  - Sensitization Testing: Determines if the device can trigger an allergic response.
  - Irritation or Intracutaneous Reactivity Testing: Evaluates the skin irritation caused by the device or its materials.
  - Systemic Toxicity Testing: Assesses the impact of the device or its leachable on the entire body system.
  - Genotoxicity Testing: Determines if the device's materials can cause damage to genetic material.
  - Implantation Testing: Evaluates the tissue response to the implanted device.

- **Chemical Characterization**: This involves identifying and quantifying chemicals present in the device, as some substances might be harmful.
- **Material-Mediated Pyrogenicity Testing:** Determines if the device or its materials can cause a fever response.
- **Extractables and Leachable Studies:** Evaluates substances that can be released from the device and potentially enter the body.

N.B.

After performing BEP, a Biological Evaluation Report (BER) documents the generated data. The BER should include Biocompatibility Risk Assessment; whereas based on the results obtained, a risk assessment is performed to determine the safety of the device.

7.3 General considerations when performing in vitro or in vivo biological testing for medical devices:

a) Any in vitro or in vivo biological safety experiments or tests should be conducted in accordance with recognized Good Laboratory Practice (GLP) regulations including, but not limited to, the assignment of competent trained staff in the conduct of biocompatibility testing.
b) When test data are provided, complete experimental data, complete to the extent that an independent conclusion could be made, should be submitted to EDA.
c) EDA recommends testing medical devices in the condition that they will be used, whenever possible. This could include final packaged devices, or as sterilized by an end user, if appropriate. If the medical device in its final finished form cannot be used for biocompatibility testing, a test article (e.g., coupons or “representative components”) may be considered. Any change in chemical composition, manufacturing process, physical configuration (e.g., size, geometry, surface properties) or intended use of the device should be evaluated with respect to possible changes in biocompatibility and the need for additional biocompatibility testing.
d) Endpoints relevant to the biocompatibility evaluation should take into account the nature, degree, frequency, duration, and conditions of exposure of the device materials to the body. This principle may lead to the categorization of devices that would facilitate the selection of appropriate endpoints for inclusion in the overall biocompatibility evaluation.
e) If the device has multiple types of exposure, information to address each exposure category identified for the device should be included, even though testing may not be necessary for every exposure category, in the overall biocompatibility assessment. For example, a pacemaker may include both a pulse generator that is implanted subcutaneously and leads that are implanted within the cardio vasculature. Therefore,

we have considered these devices to be classified as both tissues contact and blood contact devices for the evaluation of biocompatibility.

f) Positive and negative controls should be used where appropriate. The test methods used in the biological evaluation tests shall be sensitive, precise and accurate.

7.4 Animal study experience:

Data from an in vivo animal study of the medical device in its final finished form may be used in lieu of some biocompatibility tests. Testing performed in a relevant animal model can be used if the study was designed to include assessments for biocompatibility endpoints. These studies should evaluate the biological response to the test article implanted in a clinically relevant implantation site. For example, separate biocompatibility assessments for implantation, in vivo thrombogenicity, and acute, subchronic, and chronic toxicity may not be needed if these endpoints were included in the in vivo animal study design with an appropriate study endpoint, and the scientific principles and recommendations in the appropriate *ISO 10993* test method were considered and applied. If animal study data (e.g., histology, necropsy) identifies adverse biological responses, some additional biocompatibility testing may be warranted. For example, glutaraldehyde-fixed tissue heart valves may show toxic effects in animal studies as well as some standard biocompatibility assays, such as cytotoxicity and genotoxicity. These findings would usually trigger the need for additional studies, such as chemical characterization and dose ranging cytotoxicity and genotoxicity studies of suspected chemical toxins released from the device to confirm the cause of the adverse findings and to determine if additional mitigations are needed.

Because the primary purpose of the study is to evaluate safety and performance, it is recommended to consider your risk analysis (i.e., the identified risks associated with your device through bench testing, and other information, such as scientific presentations, literature review, etc.) and design the study objectives to enable study of all identified risks of your device as well as any known risks of the device type.

7.5 Special considerations for animal testing:

a) The animal model selected should be generally accepted for the study of the device type. There should be a reasonable amount of scientific evidence that the animal model has utility for the study of the device type. In some cases, there may not be an established or accepted animal model for a specific device type. We recognize that the utility of animal testing may be limited in these situations, and it may be most appropriate to proceed with limited clinical evaluation in humans, if scientifically justified. In other cases, an alternative animal model may be used and appropriately justified.

b) The rationale for the conduct of an animal study should clearly state which of the elements of your risk analysis will be addressed and why the particular animal model was selected.

c) It is recommended including a control group within the animal study design, or an explanation why a control group was not included. Additionally, when considering the number of animals needed to generate sufficient data that can support the safety and performance of a medical device, it is important to utilize sufficient animal numbers to obtain predictive outcomes. The number of animals in the study should be based on sound scientific justification with consideration for the difficulty of the model and whether one or more test article(s) and/or control article(s) can be reasonably studied in a single animal.

7.6 Biological evaluation using in-vitro & in-vivo methods:

7.6.1 In-vitro cytotoxicity

- Cytotoxicity tests employing cell culture techniques can be used to determine the cell death (e.g. cell lysis), the inhibition of cell growth, colony formation, and other effects on cells caused by medical devices, materials and/or their extracts. The overall assessment of the results shall be carried out by expert person based on the test data. Cytotoxicity data shall be assessed in relation to other biocompatibility data and the intended use of the product. The interpretation of the results of the cytotoxicity test shall take into account the classification of the device.
- If there is a cytotoxic effect, further evaluation can be performed, for example:
  a) additional tests (presence/absence of serum, changing of the level of serum in the culture medium);
  b) extract analysis (e.g. residues from sterilization and other production processes), where appropriate;
  c) concentration response analysis of dilutions;
  d) chemical characterization of leachable components,
  e) other test procedures.
- Any cytotoxic effect can be of concern. However, it is primarily an indication of potential for in vivo toxicity and the device cannot necessarily be determined to be unsuitable for a given clinical application based solely on cytotoxicity data.
- For novel materials (i.e., materials that have not previously been used in a legally marketed medical device with the same type and duration of contact), it is recommended that both direct contact and elution methods be considered. For some devices, a direct contact study may be needed to better reflect clinical use. Depending on the nature and function of the material (e.g., coatings or surface topography modifications), a non-standard direct contact study, where the cells are grown on a material surface, may be needed if no implantation data are available.
- **For more details refer to reference ISO 10993-5.**

7.6.2 Hemocompatibility

- Hemocompatibility tests can be used to evaluate, using an appropriate model or system, the effects of blood-contacting medical devices or materials on blood or blood components. One hemocompatibility test, hemolysis, determines the degree of red cell

lysis and the release of hemoglobin caused by medical devices, materials, and/or their extracts in vitro. Other specific hemocompatibility tests can also be designed to simulate the geometry, contact conditions and flow dynamics of the medical device or material during clinical applications and determine blood/material/device interactions.

- For devices having direct contact with circulating blood (regardless of contact duration), it is recommended to consider hemolysis, complement activation, and thrombogenicity testing, if not otherwise addressed during the risk assessment process.
- For devices having indirect contact with circulating blood (regardless of contact duration), it is recommended to consider only hemolysis testing, as complement activation and in vivo thrombogenicity testing are generally not needed for indirect blood contacting devices. However, for novel materials not previously used in legally marketed devices with cardiac or vascular applications, or for devices intended to release a chemical into the circulating blood, some in vitro assessment of thrombogenicity (e.g., the effect of extractables and leachables on platelets and the coagulation system) may also be needed for devices with indirect contact with blood**.**
- **For more details refer to reference ISO 10993-4.**

7.6.3 Pyrogenicity

Implants (due to their contact with the lymphatic system), as well as sterile devices having direct or indirect contact with the cardiovascular system, the lymphatic system, or cerebrospinal fluid (CSF) (regardless of duration of contact) and devices labeled as "nonpyrogenic," should meet pyrogen limit specifications. Pyrogenicity information is used to help protect patients from the risk of febrile reaction. There are two sources of pyrogens that should be considered when addressing pyrogenicity. The material mediated pyrogens, are chemicals that can leach from a medical device during device use. Pyrogens from bacterial endotoxins can also produce a febrile reaction similar to that mediated by some materials.

No single test can differentiate pyrogenic reactions that are material-mediated from those due to endotoxin contamination. Material-mediated pyrogenicity is rare. It has been observed in medical devices containing biologically-derived materials.

- **For more details refer to reference ISO 10993-11.**

7.6.4 Systemic Toxicity

- Systemic toxicity is a potential adverse effect of the use of medical devices. Generalized effects, as well as organ and organ system effects can result from absorption, distribution and metabolism of leachates from the device or its materials to parts of the body with which they are not in direct contact.
- Acute systemic toxicity tests can be used where contact allows potential absorption of toxic leachable and degradation products, to estimate the potential harmful effects of either single or multiple exposures, during a period of less than 24 h, to medical devices, materials and/or their extracts in an animal model. These tests shall be appropriate for the route of exposure. Subsequent to test sample administration in acute systemic

toxicity testing, observations are made of effects (e.g. adverse clinical signs, body weight change, and gross pathological findings) and deaths.

- Subacute and subchronic toxicity tests can be carried out to determine the effects of either single or multiple exposures or contact to medical devices, materials and/or their extracts for a period not less than 24 h to a period not greater than 10 % of the total life-span of the test animal (e.g. up to 13 weeks in rats). These tests shall be waived if available data for the chronic toxicity of the relevant materials are sufficient to allow the subacute and subchronic toxicity to be evaluated.
- Repeated exposure systemic toxicity tests provide information on health hazards likely to arise from a prolonged exposure by the intended clinical route. It might also provide information on the mode of toxic action of a substance by the intended clinical exposure route. These studies will also provide detailed information on toxic effects, target organs, reversibility or other effects and may serve as the basis for safety estimation. Results of these studies provide important information that is reflected in the extent of the guidance of clinical and anatomic pathology investigations.
- **For more details refer to reference ISO 10993-11.**

7.6.5 Irritation & Sensitization

- Some materials that are included in medical devices have been tested, and their skin or mucosal irritation or sensitization potential has been documented. Other materials and their chemical components have not been tested and may induce adverse effects when in contact with human tissue. The manufacturer is thus obliged to evaluate each device for potential adverse effects prior to marketing. Sensitization (e.g. delayed-type hypersensitivity) tests can be used to estimate the potential for contact sensitization by medical devices, materials and/or their extracts, using an appropriate model.
- There are currently three animal assays available for the determination of the skin sensitizing potential of chemicals. These include two guinea pig assays and one murine assay. So far, the two most commonly used methods for testing for skin sensitization are the Guinea Pig Maximization Test (GPMT) and the closed-patch test (Buehler test). Of these, GPMT is the most sensitive method. The closed-patch test is suitable for topical products. The third type of animal assay used is the murine Local Lymph Node Assay (LLNA), which was internationally accepted for testing single chemical as a stand-alone alternative to the guinea pig assays, and is now the preferred assay for chemicals. In some instances, guinea pig assays can be necessary for the evaluation of the sensitizing potential of certain test samples (for more details about the tests methodology, check *OECD Guidelines for testing of chemicals* and *ISO-10993-10*). Such might be true in the case of false negatives, false positives, certain metals and high molecular weight substances, which do not penetrate the skin. One should be aware that irritant activity can also result in positive lymph node responses.
- It shall be taken into consideration that, during manufacture and assembly of medical devices, additional chemical components may be used as processing aids, e.g. lubricants or mould-release agents. In addition to the chemical components of the starting material and manufacturing process aids, adhesive/solvent residues from assembly and also sterilant residues or reaction products resulting from the sterilization process may be

present in a finished product. Whether these components pose a health hazard/risk depending on the leakage or degradation characteristics of the finished products. These components shall be taken into account for their potential irritation/sensitization activity.

- For medical devices that are used as implants or external communicating devices, intradermal testing is more relevant in approaching the application and so for detection of irritation activity, intracutaneous testing shall be used. An assessment is made of the potential of the material under test to produce irritation following intradermal injection of extracts of the material.

7.6.6 Implantation effects

- Implantation tests can be used to assess the local pathological effects on living tissue, at both the gross level and microscopic level, of a sample of a material or final product that is surgically implanted or placed in an implant site or tissue appropriate to the intended application (e.g. special dental usage tests). These tests shall be appropriate for the route and duration of contact, and if performed, shall be conducted in accordance with ISO 10993-6.
- Instead of a traditional toxicology implantation study in subcutaneous, muscle, or bone tissues, a clinically relevant (e.g., brain, vascular) implantation assessment may be more appropriate for certain implant devices with relatively high safety risks. Clinically relevant implantation and muscle or subcutaneous implantation tests may be informative to the overall biocompatibility assessment of both the material components of the device and the device in its final finished form when used in its intended anatomical location.
- For implantation testing of devices with materials that are intended to degrade, we recommend that tests include interim assessments to determine the tissue response during degradation. Selection of interim assessment time points may be based on in vitro degradation testing.

7.6.7 Genotoxicity

- Genotoxicity tests can be used to assess the potential for gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by medical devices, materials and/or their extracts. A battery of *in vitro* tests is initially used. If testing is performed, it shall be conducted in accordance with *ISO 10993-3*.

- Genotoxicity testing may not be needed if chemical characterization of device extracts and literature references indicate that all components have been adequately tested for genotoxicity. Genotoxicity testing is requested when the genotoxicity profile has not been adequately established. Genotoxicity Information is requested for some devices with prolonged contact (> 24 hours to 30 days) or long-term contact (> 30 days) with blood, bone, mucosa or other tissue, or any materials that have not previously been used in legally marketed medical device applications regardless of the duration of use.
- For combination products that include a drug, if genotoxicity data are not available from the literature, the drug should be tested separately in a dose-response study (not as an extract). In addition, the final combination product should be evaluated by standard extraction

methods. If the device is tested without the drug, additional chemical characterization information should be provided to confirm that final manufacturing of the device with the drug does not introduce any new chemical moieties that could be potential genotoxins. For combination products that include a biologic, the need for genotoxicity evaluation will be reviewed on a case-by-case basis.

7.6.8 Carcinogenicity

- In the absence of any significant cancer risk, it is rare for carcinogenicity tests to be considered appropriate for medical devices. However, if it is determined that carcinogenicity testing of the final medical device is needed; it is possible that lifetime studies or transgenic models will be appropriate. It is also possible that these tests can be designed to examine both chronic toxicity and tumorigenicity in a single experimental study, as described in OECD Guideline 453.
- ISO 10993-1:2018 provides guidance on the overall biological evaluation process and considerations for selecting appropriate animal models.
- Examples where carcinogenicity testing might be needed:
    1. Implantable Medical Devices e.g. (Pacemakers, artificial joints, or vascular stents)
    2. Drug-Device Combination Products e.g. (Drug-eluting stents or contraceptive implants)
    3. Devices for Prolonged Exposure e.g. (intraocular lenses or urinary catheters)
- It is recommended that carcinogenicity potential be evaluated (usually via a risk assessment) for devices with long term contact (i.e., greater than 30-day exposure). This includes devices in contact with breached or compromised surfaces (i.e., wound healing), as well as externally communicating and implanted devices.
- Evidence of carcinogenicity is assessed by long-term in vivo animal studies (e.g., inflammation, pre-neoplastic lesions, or tumor findings in animal studies). Animal data should be relevant to assess risks in humans.

7.6.9 Reproductive and Developmental Toxicity

- If the biocompatibility evaluation identifies a known or a potential reproductive or developmental toxicity risk, and/or there is inadequate reproductive and developmental toxicity information in the literature to address the risk, testing and/or labeling mitigations will most likely be necessary. Some examples include:
    - novel implant materials if there is a potential for chemical leachables to contact reproductive organs, regardless of the type or duration of contact, and
    - device materials or components in contact with reproductive organs.
- Testing in animals of reproductive age should also be considered, if device materials may be systemically distributed (e.g., absorbable devices), and reproductive and developmental toxicity literature is not available.
- Importantly, NOAEL/LOAEL values developed to consider reproductive toxicity may be used to assess the potential reproductive toxicity of compounds released from devices that are not in direct contact with reproductive tissues.

7.6.10 Degradation

Degradation information shall be provided for any medical devices, medical device components or materials remaining within the tissue, that have the potential for degradation within the human body.

- Degradation tests shall be considered if one of the following:

a) The medical device is designed to be absorbable.
b) The device is intended to be implanted for longer than thirty days.
c) An informed consideration of the finished medical device composition indicates that toxic degradation products might be released during body contact.

- Degradation studies may not be necessary if:

a) the probable degradation products are the same substances, in the predicted quantities, and produced at a similar rate and in comparable location to those that are produced by devices that have a history of safe clinical use and/or
b) the probable degradation products are particulate and are in a physical state, i.e. size, distribution and shape, and in the predicted quantities, and produced at a similar rate and in comparable location to those that are produced by devices that have a history of safe clinical use or
c) sufficient degradation data relevant to the substances and degradation products for the intended use already exist.

When performing degradation studies, Parameters that affect the rate and extent of degradation shall be described and documented, and the mechanisms of degradation should be described. These mechanisms should be simulated in vitro to determine the rates of degradation and release of potentially toxic chemicals to estimate the exposure. It is also possible that in vivo tests will be required to assess degradation of a material.

- **For more details refer to reference ISO 10993-9.**

8. clinical investigation for medical devices

8.1. Clinical evaluation

8.1.1 What is clinical evaluation?

Clinical evaluation is a set of ongoing activities that use scientifically sound methods for the assessment and analysis of clinical data to verify the safety, clinical performance and/or effectiveness of the medical device when used as intended by the manufacturer.

8.1.2 When is clinical evaluation undertaken?

Clinical evaluation is an ongoing process conducted throughout the life cycle of a medical device. It is first performed during the development of a medical device in order to identify data that need to be generated for regulatory purposes and will inform if a new device clinical investigation is necessary, together with the outcomes which need to be studied. It is then repeated periodically as new safety, clinical performance and/or effectiveness information about the medical device obtained during its use. This information is fed into the ongoing

risk management process (according to *ISO 14971*) and may result in changes to the manufacturer's risk assessment, clinical investigation documents, Instructions for Use and post market activities.

8.2 Clinical investigation

8.2.1. What is clinical investigation?

A clinical investigation is any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety, clinical performance and/or effectiveness of a medical device for a particular indication or intended use.

This term is synonymous with 'clinical trial' and 'clinical study'. Effectiveness is the ability of a medical device to achieve clinically meaningful outcome(s) in its intended use as claimed by the manufacturer.

Clinical investigations include feasibility studies and those conducted for the purpose of gaining market approval, as well as investigations conducted following marketing authorization.

8.2.2 When should a clinical investigation be undertaken?

- When considering whether to conduct a clinical investigation for a medical device, it is essential to evaluate the specific circumstances and potential risks associated with the device's use. The need for a clinical investigation should be carefully considered, and discussions with EDA may be necessary on a case-by-case basis to ensure compliance with local regulations (Clinical Medical Research law no. 214/2021 and its executive regulations no. 927/2022) and requirements.
- Clinical investigations are necessary to provide data not available through other sources (such as literature or nonclinical testing) that is required to demonstrate compliance with the relevant essential principles (including safety, clinical performance and acceptability of benefit/risk associated with its use). When a clinical investigation is conducted, the data obtained is used in the clinical evaluation process and is part of the clinical evidence for the medical device.
- When considering the need for a clinical investigation, one should consider whether there are new questions of safety, clinical performance and/or effectiveness for the particular medical device and intended use that need to be addressed in a clinical investigation. Generally, such questions are more likely to be generated for high risk and/or novel medical devices.
- For long established technologies, the clinical investigation data that might be required for novel technologies may not be necessary. The available clinical data in the form of, for example, published literature, reports of clinical experience, post-market reports and adverse event data may, in principle, be adequate to establish the safety, clinical performance, and/or effectiveness of the medical device, provided that new risks have not been identified, and that the intended use(s)/purpose(s) has/have not changed.

8.2.3 Considerations in clarifying the need for clinical investigations:

a) Performing risk management activities such as a risk analysis will help in identifying the clinical data necessary to address residual risks and aspects of clinical performance not completely resolved by available information (e.g. design solutions, nonclinical and material/technical evaluation, conformity with relevant standards or labelling). Risk control measures include inherent safety by design, protective measures in the medical device itself or in the manufacturing process and information for safety. The decision to use a medical device in the context of a clinical procedure requires the residual risk to be balanced against the anticipated benefits of the procedure. A clinical investigation may be required to further elucidate the benefit/risk ratio in a defined patient population.

b) Conducting a proper clinical evaluation will demonstrate which clinical data are necessary and can be adequately contributed to, by sources such as literature research, prior clinical investigations (including clinical data generated in other jurisdictions), clinical experience or clinical data available from comparable devices and which clinical data should be generated from clinical investigation(s) when data are unavailable or insufficient to demonstrate conformity to the essential principles.

c) Where uncertainty exists as to whether current data are sufficient to demonstrate conformity with the essential principles, discussion with EDA or conformity assessment bodies may be appropriate. (Note: This is applicable for the introduction of a new medical device as well as for planned changes of a device, its intended use and/or claims).

8.3. Types of Clinical Investigation studies:

Medical devices can undergo three general stages of clinical development. These stages may be extremely dependent on each other and doing a thorough evaluation in one stage can make the next stage much more straightforward. To begin, medical devices may undergo an exploratory clinical stage. In this stage, the limitations and advantages of the medical device are evaluated. This stage includes first-in-human studies and feasibility studies. The next stage, the pivotal stage, is used to develop the information necessary to evaluate the safety and effectiveness of the device for the identified intended use. It usually consists of one or more pivotal studies. Finally, devices undergo a post-market stage which may include an additional study or studies for better understanding of device safety, such as rare adverse events and long-term effectiveness.

Table 1: Synopsis of clinical development stages

Regulatory status	Pre-market		Post-market	
Clinical development stages	Pilot stage	Pivotal stage	Post-market stage	
Type of design	Exploratory or confirmatory	Confirmatory		Observational
Description of clinical investigation	First in human clinical investigation Early feasibility clinical investigation Traditional feasibility clinical investigation	Pivotal clinical investigation	Post-market clinical investigation	Registry [a] Post-market clinical investigation
Burden to subject	Interventional			Non-Interventional
[a] Registry data may be used for pre-market regulatory purpose, this can also apply to post-market clinical investigation data				

8.3.1. The regulatory status:

- **Pre-market clinical investigation**

A clinical investigation carried out before market authorization of the investigational device.

- **Post-market clinical investigation**

A clinical investigation carried out following market authorization of a medical device, intended to answer specific questions related to clinical performance, effectiveness or safety of a medical device when used in accordance with its approved labelling.

8.3.2. Clinical development stages:

The clinical investigation population can be influenced by the type of clinical development stage, for example pilot stage population may come from a subgroup of the total target population for which the device is eventually indicated. However, by the time the pivotal stage is reached, the clinical investigation population should more closely mirror the target population.

- **Pilot stage**

If a pilot stage is necessary, (an) exploratory clinical investigation(s) will evaluate the limitations and advantages of the medical device and is commonly used to capture preliminary information on a medical device (at an early stage of product design, development and

validation) to adequately plan further steps of device development, including needs for design modifications or parameters for a pivotal clinical investigation.
This stage includes first in human and feasibility clinical investigations. Exploratory clinical investigations might not require pre-specified statistical hypothesis, although the design of the clinical investigation and the interpretation of the outcome can be more straightforward if statistical considerations are provided in the CIP.

- **Pivotal stage**

In the pivotal stage, one or more confirmatory clinical investigations can be conducted to provide the information necessary to evaluate the clinical performance, effectiveness or safety of the investigational device. A confirmatory clinical investigation should be adequately designed with a pre-defined hypothesis for the primary endpoint(s) and a pre-specified sound statistical method for the analysis laid out in the CIP.

- **Post-market stage**

The post-marketing stage can include additional confirmatory clinical investigations to establish clinical performance or effectiveness of the medical device in a broader population of users and subjects. Observational clinical investigations for better understanding of device safety, such as rare adverse events and long-term outcome, are also included in the post-marketing stage.

8.3.3. Type of clinical investigation design:

- **Exploratory clinical investigation**

A clinical investigation, such as a first in human or feasibility clinical investigation that might not have pre-specified primary hypothesis, and can be conducted to generate hypothesis, to be confirmed in subsequent clinical investigations.

- **Confirmatory clinical investigation**

A confirmatory clinical investigation is an adequately controlled clinical investigation in which the hypothesis of the primary endpoint(s) are stated before the start of the clinical investigation in the CIP and are analysed in accordance with the CIP (i.e. sound confirmative statistical testing is pre-specified, intended and applied).

- **Observational clinical investigation**

Clinical investigation that draws inferences about the possible effect of an intervention on subjects, but the investigator has not assigned subjects into intervention groups and has not made any attempts to collect data on variables beyond those available throughout the course of normal clinical practice and burden to the subject.

8.3.4. Descriptors of clinical investigations:

- **First in human clinical investigation**

A clinical investigation in which a medical device for a specific indication is evaluated for the first time in human subjects.

- **Early feasibility clinical investigation**

A limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g. innovative device for a new or established intended use, marketed device for a novel clinical application). It can be used to evaluate the device design concept with respect to initial clinical safety and device clinical performance or effectiveness (if appropriate) as per intended use in a small number of subjects when this information cannot practically be provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility clinical investigation can guide device modifications. An early feasibility clinical investigation does not necessarily involve the first clinical use of a device. Early feasibility clinical investigation can also be called proof of concept clinical investigation.

- **Traditional feasibility clinical investigation**

A clinical investigation that is commonly used to capture preliminary clinical performance, effectiveness or safety information of a near-final or final device design to adequately plan an appropriate pivotal clinical investigation. Because the clinical investigation of a near-final or final device design takes place later in development than an early feasibility clinical investigation, more non-clinical or prior clinical data are expected than in an early feasibility clinical investigation. A traditional feasibility clinical investigation does not necessarily need to be preceded by an early feasibility clinical investigation.

- **Pivotal clinical investigation**

A confirmatory clinical investigation designed to collect data on the clinical performance, effectiveness or safety of a device for a specified intended use, typically in a statistically justified number of human subjects. It can or cannot be preceded by an early and/or a traditional feasibility clinical investigation.

- **Registry**

An organized system that uses observational methods to collect defined clinical data under normal conditions of use relating to one or more medical devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical or policy purpose(s).

8.3.5. Burden to subjects:

- **Interventional clinical investigation**

Interventional clinical investigation is a pre- or post-market clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a CIP or diagnostic or monitoring procedures requested in the CIP are in addition to those available as normal clinical practice and burden the subject.

- **Non-interventional clinical investigation**

Non-interventional clinical investigation is a clinical investigation where the medical device is used in accordance with its approved labelling. The assignment of a subject to a particular medical device is not decided in advance by a CIP but falls within current clinical practice. The use of the medical device is clearly separated from the decision to include the subject in the clinical investigation. No additional invasive or burdensome diagnostic or monitoring procedures are applied to the subjects and epidemiological methods are used for the analysis of collected data.

8.4 The Importance of Exploratory Studies in Pivotal Study Design:

The regulatory process for medical device development involves two key stages: the exploratory stage and the pivotal stage.

During the exploratory stage, non-clinical testing, such as bench, modeling, or animal studies, is conducted to understand the device's mechanism of action and assess basic safety. The focus is on refining the device design, understanding its functionality and safety, and preparing for pivotal studies. Analytical validation for diagnostic devices is also carried out during this stage to establish performance characteristics. In addition, for diagnostic devices, the exploratory stage may be used to develop an algorithm, determine the threshold(s) for clinical decisions, or develop the version of the device to be used in the pivotal clinical study. For both in vivo and in vitro diagnostic devices, results from early clinical studies may prompt device modifications and thus necessitate additional small studies in humans or with specimens from humans. EDA should be consulted prior to initiating these studies.

Thorough evaluation during the exploratory stage ensures alignment with sponsor expectations, helps in selecting appropriate pivotal study designs, and minimizes the need for alterations during pivotal studies, which can be costly and time-consuming. Feasibility study data should not be combined with pivotal study data without prior planning.

Exploratory studies may overlap with the pivotal stage, continuing even as pivotal studies begin. For example, it may be required to continue animal testing of implanted devices at 6 months, 2 years and 3 years after implant. While the pivotal study might be allowed to begin after the six-

month data are available, additional data may also need to be collected. As another example, additional animal testing might be required if pediatric use is intended.

While the pivotal stage gathers definitive scientific evidence for safety and effectiveness, the exploratory stage is crucial for finalizing device design and determining endpoints for pivotal studies. It ensures that the device is well-prepared for the rigorous evaluation in the pivotal stage.

8.5 Considerations when determining the needed clinical investigation stage:

1) To determine which type of clinical study (early feasibility, traditional feasibility, or pivotal) is appropriate to pursue, certain factors, such as the novelty of the device, its intended clinical use, the stability of the device design, and the amount of test data available from previous nonclinical and clinical experience, needs to be taken into account.
The need for feasibility studies should be discussed with EDA, and justification should be submitted in case of not performing such studies.

2) As with all clinical studies, initiation of an early feasibility study must be justified by an appropriate benefit-risk analysis and adequate human subject protection measures.

3)Early feasibility studies may be conducted for multiple reasons, such as obtaining initial insights into:

- The clinical safety of the device-specific aspects of the procedure;
- whether the device can be successfully delivered, implanted or used;
- operator technique challenges with device use;
- human factors (e.g., difficulties in comprehending procedural steps);
- the clinical safety of the device (e.g., evaluation of device-related serious adverse events);
- whether the device performs its intended purpose (e.g., mechanical function, making intended measurements);
- device failures;
- patient characteristics that may impact device performance (e.g., anatomical limitations);
- therapeutic parameters (e.g., energy applied, sizing, dose released) associated with device use.

4) Early clinical experience obtained from an early feasibility study increases the efficiency of the device development process, as it may be used to:

- identify appropriate modifications to the procedure or device;
- optimize operator technique;
- refine the intended use population;

- refine nonclinical test plans or methodologies;
- develop subsequent clinical study protocols.

An early feasibility study is appropriate when device changes are expected and when, due to the novelty of the device or its intended use, a clinical study is expected to provide information that cannot be practically obtained through additional nonclinical assessments. An early feasibility study may be appropriate even if a device or a prototype of the device has previously been used clinically for the intended clinical use.

5) Compared to a traditional feasibility or pivotal study, less nonclinical data would generally need to be included in the Report of Prior Investigations for an early feasibility study clinical investigation application. For example, nonclinical testing using small sample sizes or short implant durations for in vivo animal studies may be sufficient to justify initiation of an early feasibility study. Under this approach, if additional and longer-term bench and animal testing are needed to support a larger clinical study of a near-final or final device design, these tests could be completed concurrently with the early feasibility study.

6) Some essential elements of a pivotal study, such as a prospective definition of study success and a prespecified data analysis plan, are not necessary for early feasibility study. In addition, an early feasibility study protocol may be subject to fewer constraints as compared to a pivotal study protocol. For example, for early feasibility studies, sequential enrollment typically would not be necessary.

8.6 . Design of the clinical investigation study:

8.6.1 General Principles of Clinical Investigation Design:

Any clinical investigation must:

- be based on the results of the clinical evaluation process;
- follow a proper risk management procedure to avoid undue risks;
- be compliant with all relevant legal and regulatory requirements;
- be appropriately planned, conducted, analysed and reported;
- follow appropriate ethical principles

The design of the clinical investigation, including the study objectives and statistical considerations, should provide the clinical data necessary to address the residual risks, including aspects of clinical performance. Some factors that may influence the extent of data requirements include, but are not limited to, the following:

- type of medical device and/or regulatory classification;
- novel technology/relevant previous experience;
- clinical application/indications;
- nature of exposure to the product (e.g. surface contact, implantation, ingestion)

- risks inherent in the use of the product (e.g. risk associated with the procedure)
- performance claims made in the medical device labeling (including instructions for use) and/or promotional materials
- component materials or substances
- disease process (including severity) and patient population being treated
- demographic, geographic and cultural considerations (e.g. age, ethnicity, gender)
- potential impact of device failure
- period of exposure to the medical device
- expected lifetime of the medical device
- availability of alternative treatments and current standard of care
- ethical considerations

8.6.2. Justification for the design of the clinical investigation

The justification for the design of the clinical investigation shall be based on the evaluation of pre-clinical data and the results of a clinical evaluation and shall be aligned with the results of the risk assessment.

The results of the clinical evaluation and the risk assessment shall be used to determine the required clinical development stages and justify the optimal design of the clinical investigation. They shall also help identify relevant endpoints and confounding factors to be taken into consideration and serve to justify the choice of control group(s) and if applicable, comparator(s), the use of randomization or blinding, and other methods to minimize bias.

The clinical investigation shall be designed to evaluate whether the investigational device is suitable for the purpose(s) and the population(s) for which it is intended. It shall be designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives, in particular the benefit-risk profile of the investigational device.

The clinical investigation should be designed to allow confirmation of the benefit-risk analysis of the investigational device as outlined in the risk management report.

Designing well-controlled prospective clinical trials of medical devices presents unique challenges that differ from those faced in studies of pharmaceuticals. For example, clinical outcomes observed in medical device studies are influenced not only by the product under evaluation and the patient, but also by the skill and discretion of the user, who is typically a health care professional but may be the patient. The impact of this third parameter—the medical device user is a variable unique to medical device studies and can be responsible for the greatest degree of variability in the clinical outcomes.
Being aware of and controlling for the user's influence on device performance is a critical variable that requires attention in designing a clinical study.

8.7. Considerations for Medical Device Study Protocols (Clinical investigation plan (CIP)):

Factors needing consideration in study protocols include:

- clear statement of objectives
- minimization of risk to subjects and those involved with the conduct of the investigation
- adverse event definitions and reporting
- study endpoints
- appropriate subject population(s)
- minimization of bias (e.g. randomization, blinding/masking, concealment of allocation)
- identification of confounding factors (e.g. concurrent therapies, co-morbidities)
- choice of appropriate controls (e.g. active control, sham, historical)
- design configuration (e.g. parallel, crossover, cohort study, single arm)
- type of comparison (e.g. superiority, non-inferiority, equivalence)
- follow-up duration and monitoring

In designing the study, statistical considerations should be prospectively specified and based on sound scientific principles and methodology. Development of a statistical plan should include consideration of the following:

- clinically relevant endpoints
- analysis population
- statistical significance levels, power
- sample size calculation and justification
- analysis methodology
- management of potential confounding factors
- procedures for multiplicity control and adjustment of error probabilities
- procedures for handling of missing, unused or spurious data, including drop-outs
- procedures for handling deviations from the original statistical analysis plan

and, as applicable:

- accounting for learning curve issues
- specification of interim analyses
- specification of subgroup analyses

The design should ensure that the statistical evaluation derived from the investigation reflects a meaningful, clinically significant outcome.

Discussion with EDA or conformity assessment bodies may be appropriate when there is uncertainty as to whether the proposed clinical investigational plan is sufficient.

8.8. Risk assessment process for potentially unacceptable risks during clinical investigation

Risks arising during the course of a clinical investigation shall be managed as follow:

a) Any person identifying an event or information that could have an impact on subjects', users' or other persons' safety, has an obligation to inform the principal investigator and the sponsor of their concerns.

b) Risks are monitored against established risk acceptability thresholds.

c) When circumstances of concern have been recognized, a preliminary risk analysis shall be performed by the sponsor in consultation with the principal investigator and, if appropriate, other advisors. The preliminary risk analysis can lead to the following outcomes.

1) The new information is adequately reflected in the existing risk assessment and the individual and overall residual risks to subjects, users, or other persons remain acceptable. The sponsor shall ensure that a rationale for this is recorded in the clinical investigation documentation.

2) Where possible, unacceptable risk or serious health threat has been identified, the sponsor shall suspend the clinical investigation immediately and the preliminary risk analysis shall be documented and notified to EDA as required, while further investigation is conducted.

d) Where a preliminary risk analysis has resulted in the recognition of the possibility of an unacceptable risk, the sponsor shall make appropriate arrangements for a comprehensive risk assessment in compliance with ISO 14971. Where appropriate, a DMC or expert advisors should provide input into or conduct the risk assessment.

e) The comprehensive risk assessment can lead to the following outcomes.

1) The new information is adequately reflected in the existing risk assessment and individual and overall residual risks to subjects, users or other persons remain acceptable. The sponsor shall ensure that a rationale for this is recorded in the clinical investigation documentation and necessary activities are performed before resuming the clinical investigation.

2) If corrective actions can be applied, including the following options:

i) **If the corrective actions do not affect the validity** of the clinical investigation, the sponsor shall revise the benefit-risk analysis to justify continuation of the clinical investigation; perform necessary activities before resuming the clinical investigation for impact on clinical investigation documents;

ii) **If the corrective actions affect the validity** of the clinical investigation, the clinical investigation shall be terminated and notified to EDA within immediately.

3) If corrective actions cannot be applied, the clinical investigation shall be terminated.

8.9. Final Study Report:

The outcome of a clinical investigation should be documented in a final study report. These forms part of the clinical data that is included in the clinical evaluation process and ultimately becomes integrated into the clinical evaluation report for the purposes of conformity assessment.

9. Combination products

A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.

Combination product is defined to include:

1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity [often referred to as a "single-entity" combination product];

2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products [often referred to as a "co-packaged" combination product];

3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labelling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose) [often referred to as a "cross-labelled" combination product]; or

4. Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect [another type of "cross-labelled" combination product].

What are some examples of combination products?

Examples of single-entity combination products (where the components are physically, chemically or otherwise combined):

- Device coated or impregnated with a drug or biologic
- Drug-eluting stent, pacing lead with steroid-coated tip, catheter with antimicrobial coating, condom with spermicide, transdermal patch
- Prefilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler)

Examples of co-packaged combination products (the components are packaged together):
- Drug or vaccine vial packaged with a delivery device
- Surgical tray with surgical instruments, drapes, and anesthetic or antimicrobial swabs
- First-aid kits containing devices (bandages, gauze), and drugs (antibiotic ointments, pain relievers)

Example a of product that may be cross-labelled combination products (components are separately provided but specifically labelled for use together):
- Photosensitizing drug and activating laser/light source

How are combination products assigned for review?

Combination products are assigned based on a determination of the "primary mode of action" (PMOA) of the combination product.

The primary mode of action is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product"

For example, if the PMOA of a device-biological combination product is attributable to the biological product, the combination is reviewed as a biological product.

Accordingly, the clinical trial application and documents to be submitted to EDA are associated with the constituent part that provides the primary mode of action (PMOA) for the combination product. The requirements for combination products should be discussed with EDA in a case-by-case basis.

The requirements for clinical trials for drug-device combination products depend on the type and classification of the combination product,

Clinical Data for Combination product:

Special considerations regarding the clinical safety and efficacy data required for each combination product.

As for example (drug eluting stent): Human toxicity Phase I studies are to be expected to determine the no observed adverse effect level (NOEL) if the medicinal substance is not approved.

10. Ethical considerations for clinical investigations of medical devices

- As a general principle, "the rights, safety and wellbeing of clinical investigation subjects shall be protected consistent with the ethical principles laid down in the Declaration of Helsinki" and the applicable regulatory requirements or other relevant standards.

- It is ethically important in deciding to conduct a clinical investigation that it should generate new data and answer specific safety, clinical performance, and/or effectiveness questions that remain unanswered by the current body of knowledge. The desire to protect human subjects from unnecessary or inappropriate experimentation must be balanced with the need to protect public health through the use of clinical investigations where they are indicated.

In all cases, however, care must be taken to ensure that the necessary data are obtained through a scientific and ethical investigational process that does not expose subjects to undue risks or discomfort. The rights, safety and well-being of subjects are paramount, and appropriate trial design and conduct is essential to generate meaningful data.

11. Risk management for medical devices

Risk management process is a Systematic approach to identifying, analysing, and controlling risks associated with medical devices throughout their entire lifecycle, from design and development to production and post-market surveillance. The primary objective of risk management in medical devices is to ensure the safety of patients and users of medical devices. By following the risk management principles and processes, manufacturers can reduce the likelihood of harm or adverse events associated with the use of medical devices as early as in the development process. This comprehensive approach also ensures that risks are continually monitored and managed throughout the device's life. This can lead to improved product quality, reliability and performance; ultimately benefiting patients and healthcare providers.

In the phase of preclinical assessment of medical devices, the biological evaluation of any material or medical device intended for use in humans shall form part of a structured biological evaluation plan within a risk management process in accordance with ISO 109931-1. This risk management process involves identification of biological hazards, estimation of the associated biological risks, and determination of their acceptability.

In the phase of clinical evaluation, Risks associated with the investigational device and its related clinical procedure shall be estimated in accordance with ISO 14971 prior to design and conduct of a clinical investigation. Risk management principles shall be applied to both the planning and the conduct of clinical investigations, in order to ensure the reliability of the clinical data generated and the safety of subjects.

The risk management process associated with a clinical investigation allows the hazards and hazardous situations associated with the investigational device to be identified. The associated risks are estimated (risk analysis) and evaluated (benefit-risk analysis), and risks are reduced to an acceptable level where necessary (risk control). The effectiveness of risk control is evaluated throughout the product's lifecycle including during clinical investigations. The sponsor shall identify, assess and control risks associated with clinical investigation processes to ensure the ethical and scientific conduct of the clinical investigation and the credibility of the clinical investigation results. The clinical investigation should provide sufficient clinical data on the acceptability of benefit risk ratio, and this is documented in the risk management report.

11.1 General requirements for risk management system

Risk management process:

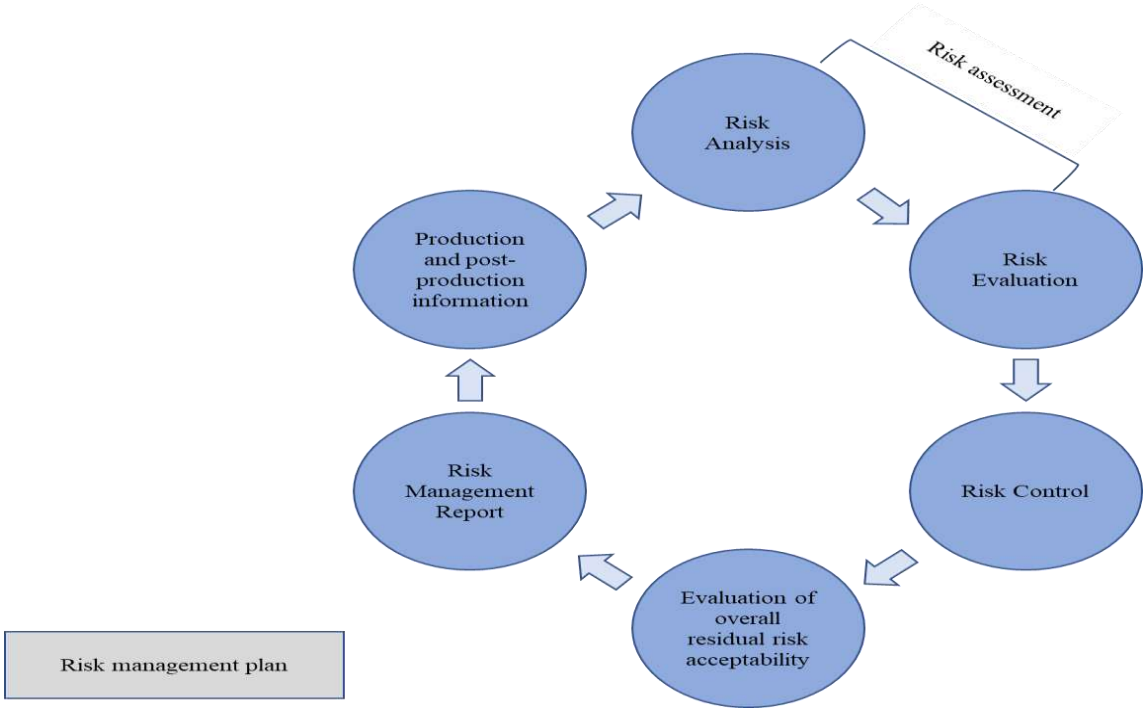
The manufacturer shall establish, implement, document and maintain an ongoing process for:

a) Identifying hazards and hazardous situations associated with a medical device;
b) Estimating and evaluating the associated risks;
c) Controlling these risks, and
d) Monitoring the effectiveness of the risk control measures.

The process of risk management shall include the following elements:
- Risk analysis;
- Risk evaluation;
- Risk control;
-Evaluation of overall RR;
-Risk management review (report);
- Production and post-production activities.

A documented process within a quality management system can be used to address safety in a systematic manner, in particular to enable the early identification of hazards and hazardous situations in complex medical devices.
Depending on the specific life cycle phase, individual elements of risk management can have varying emphasis. Also, risk management activities can be performed iteratively or in multiple steps as appropriate to the medical device.
The risk management report documents the process of benefit to risk assessment and demonstrates that the device is considered safe.
The risk management process shall be performed in accordance *to ISO 14971: Medical devices – "Application of risk management to medical devices",* which provides detailed information on performing the risk management plan.

Figure (2) A Schematic Representation of Risk Management process.



11.2 Factors to be Considered when Making Benefit-Risk Determinations:

11.2.1 Assessment of the Benefits of Devices:

A. Extent of the probable benefit(s): the following factors are to be considered when assessing the extent of probable benefits for investigational medical devices:

- **The type of benefit(s):** examples include but are not limited to the device's impact on clinical management, patient health, and patient satisfaction in the target population, such as significantly improving patient management and quality of life, reducing the probability of death, aiding improvement of patient function, reducing the probability of loss of function, and providing relief from symptoms. These endpoints denoting clinical benefit are usually measured directly, but in some cases may be demonstrated by use of validated surrogate endpoints. For diagnostics, a benefit may be assessed according to the public health impact of a particular device, due to its ability to identify a specific disease and therefore prevent its spread, predict future disease onset, provide earlier diagnosis of diseases, or identify patients more likely to respond to a given therapy.
- **The magnitude of the benefit(s):** benefit is often assessed along a scale or according to specific endpoints or criteria (types of benefits), or by evaluating whether a pre-identified health threshold was achieved. The change in participants' condition or clinical management as measured on that scale, or as determined by an improvement or worsening of the endpoint, is what allows to determine the magnitude of the benefit in participants. Variation in the magnitude of the benefit across a population may also be considered.
- **The probability of the patient experiencing one or more benefit(s):** based on the data provided, it is sometimes possible to predict which patients may experience a benefit, whereas other times this cannot be well predicted. A benefit may be experienced only by a small portion of patients in the target population, or, on the other hand, a benefit may occur frequently in patients throughout the target population. It is also possible that the data will show that different patient subgroups are likely to experience different benefits or different levels of the same benefit. If the subgroups can be identified, the device may be indicated for those subgroups. In some cases, however, the subgroups may not be identifiable. In addition, magnitude and probability are considered together when weighing benefits against risks. That is, a large benefit experienced by a small proportion of participants may raise different considerations than does a small benefit experienced by a large proportion of participants. For example, a large benefit, even if experienced by a small population, may be significant enough to outweigh risks, whereas a small benefit may not, unless experienced by a large population of participants.
- **The duration of effect(s) - (i.e., how long the benefit can be expected to last for the patient):** some treatments are curative, whereas, some may need to be repeated frequently over the patient's lifetime. Treatments that must be repeated over time may introduce greater risk, or the benefit experienced may diminish each time the

treatment is repeated.

11.2.2 Assessment of the Risks of Devices

Extent of the probable risk(s)/harm(s): the extent of the probable risk(s)/harm(s) are assessed through the following factors:

- **Severity, types, number and rates of harmful events associated with the use of the device:** (as per described in the safety reporting section as device/ non-device related adverse events).
- **Probability of a harmful event:** the proportion of the intended population that would be expected to experience a harmful event. EDA would factor whether an event occurs once or repeatedly into the measurement of probability.
- **Duration of harmful events (i.e., how long the adverse consequences last): some** devices can cause temporary, minor harm; some devices can cause repeated but reversible harm; and other devices can cause permanent, debilitating injury. EDA would consider the severity of the harm along with its duration.
- **Risk from false-positive or false-negative results for diagnostics**

N.B.: The number of different types of harmful events that may result from using the device and the severity of their aggregate effect are also considered. When multiple harmful events occur at once, they have a greater aggregate effect. For example, there may be a harmful event that is considered minor when it occurs on its own, but, when it occurs along with other harmful events, the aggregate effect on the patient can be substantial.

11.2.3 Additional Factors to be considered in the Assessment of the Probable Benefits and Risks of Devices

- **Uncertainty: there is never 100% certainty when determining reasonable assurance of** safety and effectiveness of a device. However, the degree of certainty of the benefits and risks of a device is a factor to be considered when making benefit-risk determinations. For example, Factors such as poor design or poor conduct of clinical trials, or inadequate analysis of data, can render the outcomes of the study unreliable, and therefore affect the certainty of the generated data.

In addition, the generalizability of the trial results to the intended treatment and user population is important. In general, it is important to consider the degree to which a clinical trial population is representative of the intended marketing or target population.

- **Patient-centric assessments and patient-reported outcomes (PROs):** patient-centric metrics such as validated health-related quality of life measures and other Patient-Reported Outcomes (PROs) (e.g., scales or scores indicating patient's experience of pain or function) can be helpful for patients and health care

practitioners and provide better insights when determining the device's benefits.

- **Characterization of the disease**: the treated or diagnosed condition, its clinical manifestation, how it affects the patients who have it, how and whether a diagnosed condition is treated, and the condition's natural history and progression (i.e., does it get progressively better or worse for the patient and at what expected rate) are all important factors that EDA considers when characterizing disease and determining benefits and risks

- **Patient perspectives:** Generally, risk tolerance will vary among patients, and this will affect individual patient decisions as to whether the risks are acceptable in exchange for a probable benefit. patient preference assessments should take into account both the patient's willingness and unwillingness to use a device or tolerate risk in exchange for probable benefit, and/or evaluate how patients view trade-offs between benefits and risks of various treatment options.

12. Safety reporting in clinical investigation studies of medical devices[1]

12.1 Reportable events (also known as incidents):

a) Any serious adverse event that affects the subjects involved in the clinical investigation regardless its causality.
b) Any device deficiency that might have led to a serious adverse event
c) Any new findings in relation to any event referred to in points 1) and 2).
d) Any serious adverse event in PMCF (post market clinical follow up) clinical investigations, where the marketed device is being used in a new indication other than the intended use, tested on new populations, or undergoes any design changes that requires interventional clinical investigations.
e) For local non-serious adverse events, Line Listing should be submitted along with the progress follow-up report [1].

Note: For pre-market clinical investigations involving CE marked comparator devices used within their intended purpose, SAEs occurring in or to subjects that are in the comparator arm of an investigation shall also be reported in accordance with this guideline.

[1]For investigational medical devices, in addition to this guideline; Applicant shall follow *EDA (Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority,* for specific EDA timelines and procedures of safety reporting.

f) Other safety issues also qualify for expedited reporting to Bio-Inn EDA, in some cases or special conditions - where the incident/event led to a SAE - as:

i) **An event has occurred typical problems that might include deficiencies in labeling, instructions or packaging, defective components, performance failures, poor construction, or design. The events include, but are not limited to:**

-A malfunction or deterioration in the characteristics or performance: a failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer's instructions.
-False positive or false negative test result falling outside the declared performance of the test.
-Interactions with other substances or products.
-Degradation/destruction of the device (e.g. fire).
-Inappropriate therapy.
-An inaccuracy in the labeling, instructions for use and/or promotional materials. Inaccuracies include omissions and deficiencies.

ii) **The device is suspected to be a contributory cause of the incident.** in assessing the link between the device and the incident the manufacturer/sponsor should take account of:

-The opinion based on available evidence of PI.
-The results of the PI's own preliminary assessment of the incident.
-Evidence of previous, similar incidents.
-Other evidence held by the manufacturer/sponsor.

This judgment may be difficult when there are multiple devices and drugs involved. In complex situations, it should be assumed that the device may have caused or contributed to the INCIDENT and the MANUFACTURERs should err on the side of caution.

Reportable events occurring in other countries:

- If several clinical investigations (CI) are conducted with the same device, SAEs that take place in all CIs of this device worldwide should be submitted every 6 months in a global SUSAR line listing.
- Six Months Line listing of global SUSARs should be reported as long the clinical medical research is authorized in Egypt even if it has not started yet.

- Events occurring in other Countries after the participating Egyptian sites have closed shall continue to be reported.

12.2 Seriousness criteria:

- An event is considered serious which led, or might have led, to one of the following outcomes:

- Death of a subject involved in clinical investigation,
- Serious deterioration in state of health of a subject,
- life-threatening illness,
- permanent impairment/disability of a body function or permanent damage to a body structure,
- a condition necessitating medical or surgical intervention to prevent life threatening illness or permanent impairment (e.g.: clinically relevant increase in the duration of a surgical procedure),
- a condition that requires hospitalization or significant prolongation of existing hospitalization,
- Any indirect harm [2] as a consequence of an incorrect diagnostic or IVD test results that is being investigated in the clinical investigation plan (CIP), or any event that is considered as a serious public health threat[3]. (In assessing whether events represent a serious health threat, discussion should be undertaken with the EDA and consideration should be given to the risk analysis described in the CIP).
- fetal distress, fetal death or any congenital abnormality or birth defects

N.B: a planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health is not considered to be a SAE.

- Other reported conditions expected side effects which meet all the following criteria:
  -Clearly identified in the manufacturer's labeling.
  -Clinically well known as being foreseeable and having a certain qualitative and quantitative predictability when the device is used and performs as intended.
  -Documented in the device master record, with an appropriate risk assessment, prior to the occurrence of the incident.
  -Clinically acceptable in terms of the individual patient benefit.

[2] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition).
[3] Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, e.g. human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD). These concerns may be identified by either the Egyptian health authorities or the MANUFACTURER

12.3 Causality assessment and relationship:

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. For the purpose of harmonizing reports, each SAE will be classified according to **six** different levels of causality; following are the most common practice unless otherwise specified in the protocol:

1. Causal relationship (certain)
2. Probable/ likely
3. Possible
4. Unlikely
5. Not related
6. Un-assessable

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device, the comparator or the investigation procedure:

1. Causal relationship (certain): The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- The event has a temporal relationship with investigational device use/application or procedures;
- The event involves a body-site or organ that:
• The investigational device or procedures are applied to,
• The investigational device or procedures have an effect on;
- The serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- Harm to the subject is due to error in use;
- The event depends on a false result given by a diagnostic investigational device[4]

[4] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed

- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

2. Probable (likely): The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

3. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment).

4. Unlikely: A clinical event with a temporal relationship to the use of the investigational device, comparator or with the procedures that makes a causal relationship with any of them improbable (but not impossible), and in which another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors) provide more plausible explanations.

5. Not related: Relationship to the device, comparator or procedures can be excluded when:
- The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- The SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- The event involves a body-site or an organ that cannot be affected by the device or procedure;
- The serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- The event does not depend on a false result given by a diagnostic investigational, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition).

6. Un-assessable: A report suggesting an adverse drug reaction, which cannot be judged because the information is insufficient or contradictory and which cannot be supplemented or verified.

- During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there.
- The above considerations apply also to the serious adverse events occurring in the comparison group.
- The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.
- The occurrence of unanticipated related events could suggest that the clinical investigation might involve subjects to an increased risk of harm than that which was expected beforehand, so particular attention shall be given to the causality evaluation of unanticipated serious adverse events.
- The serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation) should be distinguished by the sponsor & the investigator. The serious adverse event can be related to both the procedure and the device, or it can be related only to the procedure or only to the device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.
- When it is unclear whether an event is related to the device or to the procedure, the investigator should:
  - Set the Relationship to device to possible (or higher)

  AND
  - Set the Relationship to procedure to possible (or higher),

Since it is the healthcare provider who performs the procedures and manages/handles the medical device(s), then the causality assessment of this healthcare provider should prevail.

12.4 Timing of Reporting:

Upon becoming aware of events meeting the reportability criteria, the following should be used to establish the timeline under which events of various levels of severity are to be reported:

➢ Fatal or life-threatening serious adverse events (including serious adverse events which have been determined to represent a serious health threat to the study population), whether anticipated or unanticipated should be notified to EDA within 24 hours starting from the time at which site is notified/aware of the event/threat. The immediate notification should contain the following information:

• The study number, the site number and name, the subject's identification number, the investigational device (including the device type as per assessed in the CIP), The date of the SAE occurrence, Description of the SAE.

➢ This immediate notification should be followed by an initial, as complete as possible report, within 7 calendar days starts from the site is notified of the event. The initial report should include:

• Causality assessment, A narrative about all diagnostic tests and examinations performed, treatment procedures, and medications/devices administered to the study subject to the date of the report, Expectedness of the serious adverse event, The Outcome.

➢ Each initial report must lead to a follow up and a final report whenever further information becomes available, unless the initial and the final report are combined into one report and all the data in the safety reporting format are complete.

➢ Non-fatal, non-life threatening serious adverse events, whether anticipated or unanticipated should be notified to EDA as soon as possible and not later than 7 calendar days starting from the time at which site is notified/aware of the event. This expedited notification should contain the following information:

• The study number, the site number and name, the subject's identification number, the investigational device (including the device type as per assessed in the CIP), The date of the SAE occurrence, Description of the SAE, The severity of the SAE, Causal Relationship and Expectedness of the SAE

➢ The notification should be followed by as complete as possible report within additional 8 calendar days. This report should include:

• Causality assessment, A narrative about all diagnostic tests and examinations performed, treatment procedures, and medications administered to the study participant to the date of the report, Expectedness of the serious adverse event, The Outcome.

Special Conditions:

1. ***Medicinal product/device, biologic product/device combinations*:** Serious adverse events/device deficiencies for combination products that involve drugs or biologics where their action is ancillary to an investigational medical device should be reported in line with the principles set out in this guideline.
2. ***Controlled clinical investigations:*** whether unblinded or blinded clinical investigation using a marketed medical device as a control, all SAEs and device deficiencies leading to SAE of the control should be reported in line with this guideline and EDA guideline for good regulatory oversight (safety reporting section).
3. ***Implantable medical devices:*** all SAEs including device deficiencies occurring with devices implanted in a patient in a clinical investigation setting are reportable as above.
4. ***Not all incidents lead to death or serious deterioration*** in health. the non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel. it is sufficient that: An incident associated with a device happened, and the incident was such that, if it occurred again, it might lead to death or serious deterioration in health, or any of the other seriousness criteria.

- ## Content of Reports:

Please refer to (annex I) "safety reporting format for medical devices in clinical investigation".
The reporting form can be used by the Applicant for the purpose of initial, follow up, and final reporting.

Reporting of all Serious Adverse Events is sent to Bio Inn within the specified timelines[5]. However, the PI can delegate this task to the sponsor, manufacturer or CRO. Reporting – along with the delegation of the PI to sponsor, manufacturer or CRO - is sent to email address of protocols & clinical studies follow up administration: (bio.ct@edaegypt.gov.eg).

- ## Types of reports:

A. Initial report
defined as the first information submitted by the PI (or its delegated) about a reportable event, but the information is incomplete and supplementary information will need to be submitted.

B. Follow-up report
defined as a report that provides supplemental information about a reportable event that was not previously available.

[5] For more details on the specified timelines please refer to annex IV in EDA (Guideline for Good Regulatory Oversight of Clinical Trials by Egyptian Drug Authority, EDREX.GL.Bioinn.006)

C. Final report

defined as the last report that the PI (or the delegated entity) expects to submit about a reportable event. It is a written statement of the outcome of the investigation and of any action. In some cases, a final report may also be the first report.

Examples of actions may include:
No action, additional surveillance of devices in use, preventive action on future production, Field Safety Corrective Action (FSCA).

Field Safety Corrective Action (FSCA)

A field safety corrective action is an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. Such actions should be notified via a field safety notice.

In such case where the medical device used in the CI (whether a marketed device used in a new indication, or a marketed device used as a comparator), the manufacturer/authorized representative is required to report to Bio-Inn, EDA any technical or medical reason leading to a systematic recall of devices of the same type by the manufacturer.

Those reasons are:

- any malfunction
- deterioration in the characteristics
- deterioration in the performance of a device,
- any inadequacy in the instructions for use all and/or any of the above reasons that might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health.

A. General principles of FSCA:

Removals from the market for purely commercial non-safety related reasons are not included in the scope of this guideline.
FSCA taken on a basis of incidents occurred outside Egypt and affecting devices marketed and used in clinical investigations that are approved inside Egypt are included in this guideline.
FSCA should be notified via a field safety notice.

B. The FSCA may include:

1. The return of a medical device to the supplier;
2. Device modification;
3. Device exchange;
4. Device destruction;

5. Retrofit of manufacturer's modification or design change;
6. Advice given by manufacturer regarding the use of the device (e.g. where the device is no longer on the market or has been withdrawn but could still possibly be in use e.g. implants or change in analytical sensitivity or specificity for diagnostic devices).

N.B.: In some cases, this action may be discussed with EDA, to perform an amendment so that the changes are reflected in the clinical investigation plan. This can also be based on Recommendations of the Data Monitoring Committee where relevant for the safety of the subjects.

Field Safety Notification

The manufacturer/authorized representative should issue a notification to the competent authorities of all countries affected at the same time and also to Bio-Inn, EDA. This notification should include all relevant information necessary to monitor the FSCA taken regarding the medical device used in clinical investigation, e.g.:

-Affected devices and serial / lot / batch number range, and whether any of them is used in the clinical investigation performed inside Egypt

-Identity of the manufacturer

-Relevant parts from the risk analysis.

-Background information and reason for the FSCA (including description of the device deficiency or malfunction, clarification of the potential hazard associated with the continued use of the device and the associated risk to the patient, USER or other person and any possible risks to patients associated with previous use of affected devices).

-Description and justification of the action (corrective/preventive).

13. References:

13.1 Regulation (EU) 2017/745 of the European parliament and of the council of 5 April 2017, on medical devices, amending directive 2001/83/EC, Regulation (EC) no 178/2002 and Regulation (EC) no 1223/2009 and repealing council directives 90/385/EEC and 93/42/EEC

13.2 Regulation (EU) 2017/746 of the European parliament and of the council of 5 April 2017, On In Vitro Diagnostic Medical Devices and Repealing Directive 98/79/EC and Commission Decision 2010/227/EU

13.3 Regulation (EC) No178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (MDR)

13.4 European Medicines Agency Guideline on Clinical Evaluation of Diagnostic Agents, London, 26 June 2008

13.5 Design Considerations for Pivotal Clinical Investigations for Medical Devices Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration, November 7, 2013

13.6 Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process "Guidance for Industry and Food and Drug Administration September 8, 2023.

13.7 General Considerations for Animal Studies Intended to Evaluate Medical Devices, Guidance for Industry and Food and Drug Administration, March 28, 2023.

13.8 GHTF/SG5/N6:2012, “Clinical Evidence for IVD medical devices – Key Definitions and Concepts” IMDRF MDCE WG/N57FINAL:2019, “International Medical Device Regulators Forum, clinical investigation”

13.9 GHTF/SG5/N6:2012, "Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices"

13.10 IMDRF/IVD WG/N64FINAL:2021, “Principles of In Vitro Diagnostic (IVD) Medical Devices Classification”

13.11 GHTF/SG1/N77:2012, “IMDRF, Principles of Medical Devices Classification”

13.12 Application of risk Management to medical devices (EN ISO 14971:2019)

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