Medical Device Toolkit

Clinical Investigations in Ireland
&
European Medical Device Regulations

Rev.1, May 2023

Health Research Board
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Scope of Toolkit

- The toolkit is intended to provide information to investigators wishing to conduct clinical investigations of medical devices in Ireland. The information may be beneficial for both academic and commercial investigators.
- In addition, the toolkit provides a high-level overview of the primary international standards and European regulations applicable to all medical device developers. Finally, medical device development terminology and considerations are introduced, including classification, risk management and quality management systems.
- However, the tool kit does not go in-depth into conformity requirements to prepare a device for clinical investigations. Therefore, the toolkit should not replace professional advice from legal, regulatory, quality and design control experts.

The Irish Review System

To conduct a clinical Investigation in Ireland you must:

- *Apply to the Health Products Regulatory Authority (HPRA) and*
- *Apply to the National Research Ethics Committee for Medical Devices (NREC-MD)*

Clinical Investigations in Ireland

The Health Products Regulatory Authority (HPRA) acts on behalf of the Irish government to regulate human and veterinary medicines, clinical trials, medical devices, controlled drugs, blood and blood components, tissues and cells, and cosmetic products.

The HPRA is the only Irish national competent authority and is responsible for enforcing the European Medical Device Regulations (Medical Devices Regulation (EU) 2017/745), providing authorisation of clinical investigations, and monitoring the safety and compliance of medical devices with national laws.

Guide to Medical Device Clinical Investigation application to HPRA

1 Preliminary Meeting with HPRA

A preliminary meeting is typically set-up for early-stage 'start-up' companies, to understand the HPRA role and the regulatory requirements of the pre-market phase of device development.

2 Pre-submission Meeting with HPRA

Typically, sponsors who plan to submit a clinical investigation application get answers to any question at a presubmission meeting before submitting an application.

3 Submit Application

Device Type

- Non-CE marked or CE marked outside intended use (*Article 62 MDR Application)
- CE marked but additional burden or invasiveness (*Article 74 MDR Application)
- All other studies outlined in Part 3, Article 14 of S.I. 261 2021 (*Article 82 MDR Application)

*See Slide "Clinical Investigation Under MDR" for Article details

Clinical Investigations in Ireland

The National Office for Research Ethics Committees was set up to provide a single, independent ethics opinion on whether research or investigations are ethical to protect the safety, dignity and well-being of participants.

The National Research Ethics Committee for Clinical Investigations of Medical Devices and Performance Studies of In Vitro Diagnostic Medical Devices (NREC-MD) review submissions of ethics applications regulated under the MDR (Medical Devices Regulation (EU) 2017/745).

Clinical Investigation application to the NREC-MD

1 Submit Application

Applicants must submit the NREC-MD application form and checklist using the NREC-MD documentation templates.

Submission cut-off dates

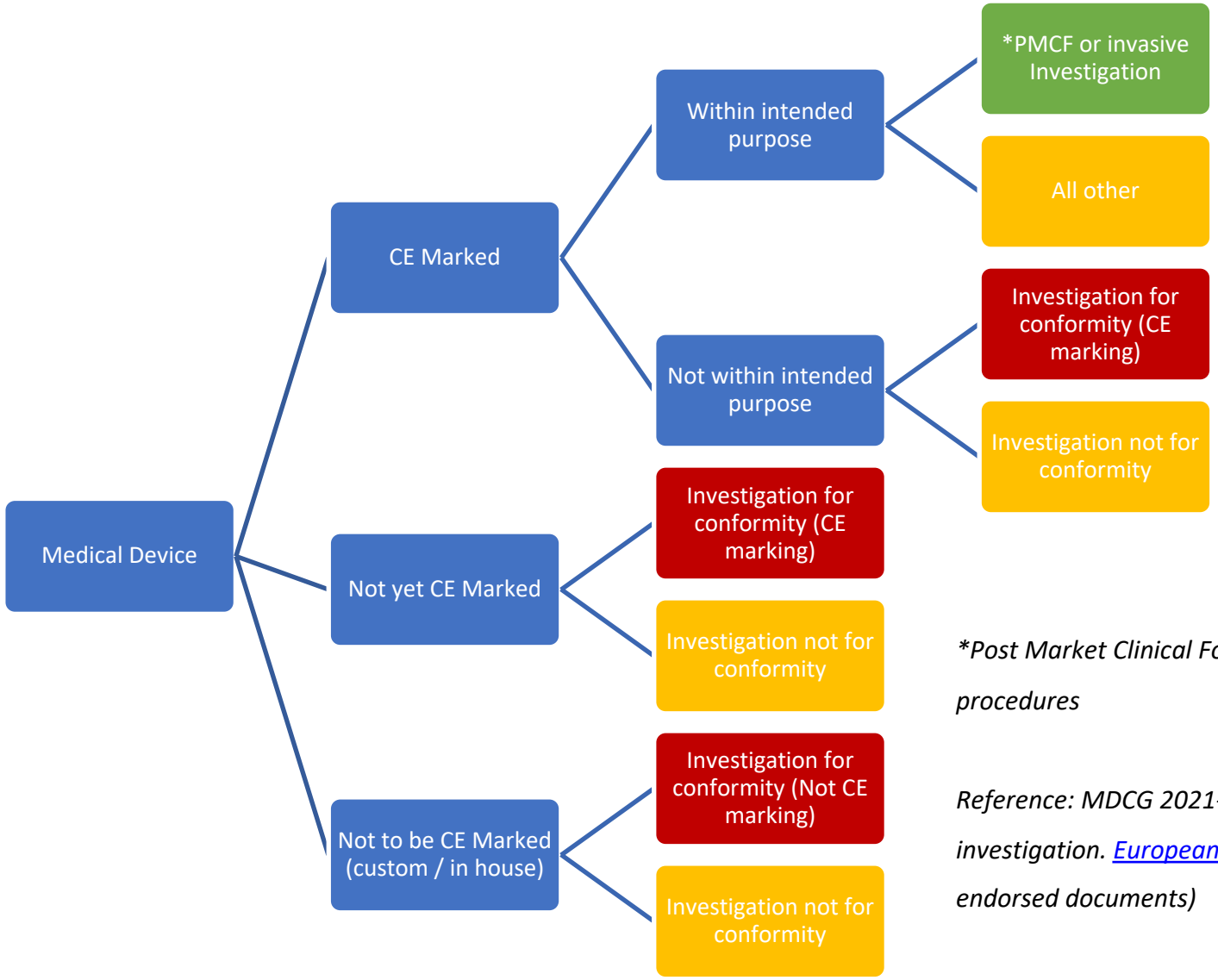
2 Application Validation

Notification that the application is 'Valid' or 'Invalid' is received **within seven days** of validation.

3 Ethics Opinion Issued

Ethics opinion is issued **within 55 days** from the notification of validation

The Regulatory Path for Clinical Investigations under MDR



Article 62 of the MDR

Article 74(1) of the MDR

Article 82 of the MDR

Plus, relevant national provisions which may apply

**Post Market Clinical Follow-Up (PMCF) investigation with additional burdensome and/or invasive procedures*

Reference: MDCG 2021-6 Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation. European Guidance Documents - (Medical Device Coordination Group (MDCG) endorsed documents)

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Clinical Investigation

IMDRF Definition: 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.

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Key Considerations - Clinical Investigations

- Clinical data from a clinical investigation is used in the clinical evaluation process and is part of the clinical evidence for the medical device.
- Clinical investigations are necessary to provide data not available through other sources (such as literature or nonclinical testing) required to demonstrate compliance with the relevant Essential Principles (including safety, clinical performance and acceptability of benefit/risk associated with its use) *(Reference IMDRF MDCE WG/N57 - Clinical Investigation, 2019 (formerly GHTF/SG5/N3:2010))*
- To comply with the MDR in Europe, a clinical investigation is the most direct way to generate clinical data for CE marking. However, the regulations allow for **sourcing clinical data** (for example, from the literature) for a device where equivalence can be demonstrated to the device in question *(Reference MDCG 2020 -5)*.
- Regulatory authorities or conformity assessment bodies can help to determine if current data are sufficient to support the clinical evaluation process.

Clinical Investigation Application/Notification Documents and Registration

- Medical Device Regulation (EU) 2017/745 Annex XV, Chapter II, lists the documentation that must accompany the clinical investigation application. In addition, the guidance Clinical Investigation application/ notification documents (MDCG 2021-8) contains links to document templates.
- A description of the clinical investigation is required in a publicly accessible database before recruitment starts per ISO 14155:2020 and the Declaration of Helsinki.
- Submission using the European database (electronic system) on medical devices (EUDAMED) and a Summary of Safety and Clinical Performance (SSCP) for implantable and class III devices are required under MDR (Article 73 and Article 32 of MDR).
    - *The EUDAMED system is currently being developed and expected to commence in 2024. Once established, EUDAMED aims to provide a living picture of the lifecycle of medical devices available in the EU.*
- Currently, in Ireland, the HPRA require Common European Submission Portal (CESP) registration and document submission through the CESP. In addition, the HPRA will issue a CIV-ID number (a Union-wide unique single identification number). This can be used for the same study across any member state.

MDCG 2021-6 Q&A Regarding Clinical Investigation

- The guidance document "Questions and answers relating to clinical investigations (MDCG 2021-6)" details frequently asked questions and contains useful annexes. For example:
  - Question 6 addresses early pilot stage studies, e.g. First in Man (FIM) investigations, and discusses the use of MDR **Article 82,** which allows a national regulatory pathway if the study is not intended to support conformity assessment;
  - Annex 1 illustrates the regulatory path for different types of devices (i.e. indicates if Articles 62, 74 or 82 should be followed) and
  - Annex 2 provides examples of modifications (to the clinical investigation) that may be interpreted as substantial, and the actions required if a substantial modification is made to the clinical investigation.

European Guidance Documents - (Medical Device Coordination Group (MDCG) endorsed documents)

Medical Device Regulations *MDR (EU 2017/745)*

The MDR entered into force in May 2017 alongside in-vitro diagnostic MDR. With effect from 26 May 2021, the MDR (EU 2017/745) replaced directives 90/385/EEC and 93/42/EEC.

Medical Device Regulations in Europe (Agency / Authorities / Bodies)

- European Medicines Agency (EMA)
  - Agency of the European Union (EU) responsible for scientific evaluation, supervision and safety monitoring of medicines.
  - Medical devices are regulated at EU Member State level, but the European Medicines Agency (EMA) is involved in the regulatory process.
  - The EMA Provide scientific opinions to notified bodies through consultation and is involved in conformity assessments of higher-risk medical devices.
- **Designated National Competent Authorities - the Health Products Regulatory Authority (HPRA) in Ireland**
  - Body acting on behalf of the government. Responsible for enforcing the MDR, providing authorisation of clinical investigations and monitoring the safety and compliance of medical devices with national laws.
- **Notified Bodies** (e.g., BSI, TUV, NSAI)
  - Designated and accredited by the EU Member States.
  - Conduct conformity assessments to allow companies to obtain CE certification.

MDR Transition

The MDR (Medical Devices Regulation (EU) 2017/745) entered into force in May 2017 alongside *in-vitro* diagnostic MDR. With effect from 26 May 2021, the MDR **replaced Medical Device Directives** 90/385/EEC and 93/42/EEC.

See the Links below for MDR Support and Information

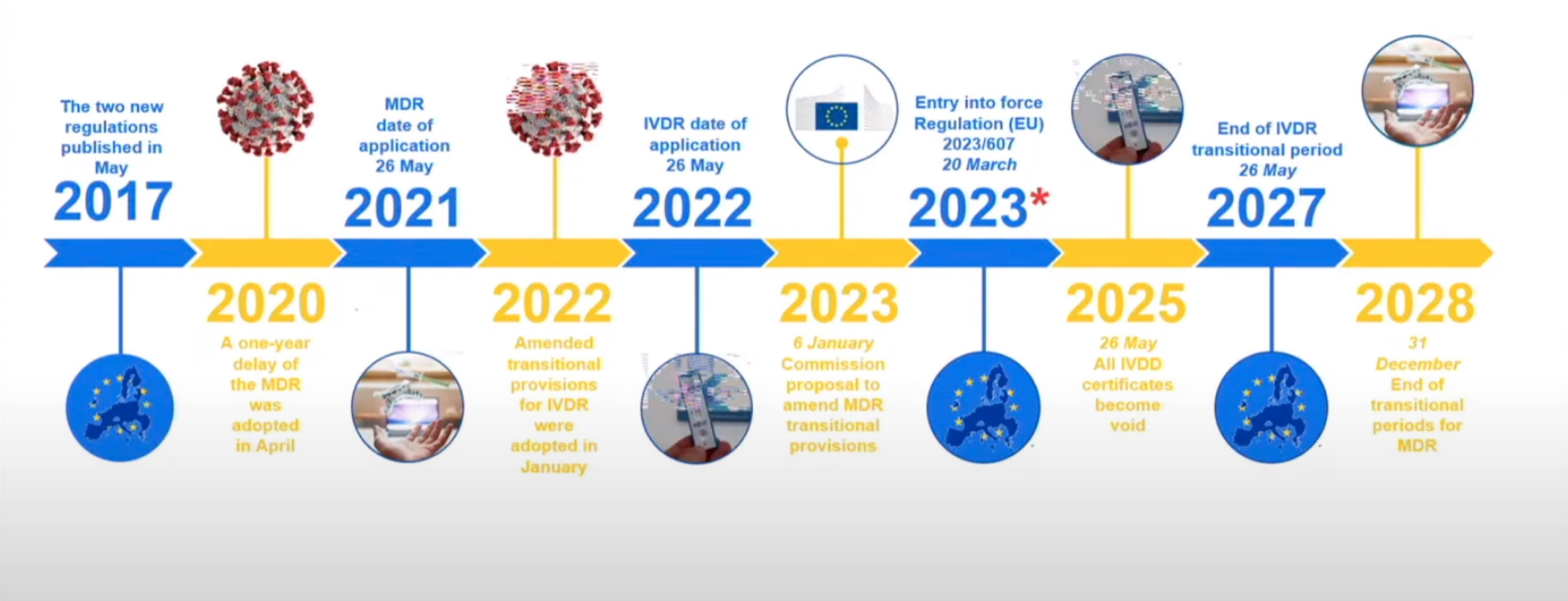
European Commission

- ➔ Dedicated Factsheets
- ➔ Rolling Plan
- ➔ Guidance Documents - (Medical Device Coordination Group (MDCG) endorsed documents)

HPRA

- ➔ MDR transitional provisions
- ➔ Qualification and classification of medical devices
- ➔ A guide to clinical Investigations in Ireland

Timelines for MDR Roll-out



Reference: IMDRF public presentation ("Update on EU Regulatory Developments. IMDRF – 23 Stakeholder session 28th Mar 2023").

The International Medical Device Regulator's Forum (IMDRF) documents support regulatory harmonisation (previously known as Global Harmonization Task Force (GHTF)).

Relevant IMDRF Working Group Technical Documents

The International Medical Device Regulator's Forum (IMDRF) documents support global regulatory harmonisation, previously known as Global Harmonization Task Force (GHTF), have produced the following technical documents that relate to clinical investigations:

- IMDRF MDCE WG/N57 - Clinical Investigation, 2019 (formerly GHTF/SG5/N3:2010)
- IMDRF MDCE WG/N55 - Clinical Evidence - Key Definitions and Concepts, 2019 (formerly GHTF/SG5/N1R8:2007)
- IMDRF MDCE WG/N56 - Clinical Evaluation, 2019 (formerly GHTF/SG5/N2R8:2007)
- IMDRF/SaMD WG/N41 - Software as a Medical Device (SaMD): Clinical Evaluation, 2017
- IMDRF/MDCE WG/N65 - Post-Market Clinical Follow-Up Studies, 2021 (formerly GHTF/SG5/N4:2010).

Authoring Working Groups: Medical Device Clinical Evaluation (MDCE) and Software as a Medical Device (SaMD)

Irish Regulations

Irish Medical Device Regulations 2021 (S.I. No. 261 of 2021) came into operation in May 2021 alongside the MDR. The regulation details how the MDR is implemented in Ireland and the functions and powers of the HPRA and the National research ethics committee. The regulation includes:

- Requirements for implantable devices and processes for single-use devices (part 2)
- Clinical investigation requirements (part 3)
- Offences, penalties, compliance and enforcement details (part 4)
- Revocations and transitional provisions details (part 5)

Other Irish Regulations include

- S.I. 547/2017 European Union (Medical Devices and In Vitro Diagnostic Medical Devices) Regulations 2017 and,
- S.I. 691/2021 Medical Devices (Registration) Regulations 2021

Irish Regulations

National requirements and procedures for clinical investigations are detailed in part 3 of (S.I. No. 261 of 2021) and includes:

- Requirements of qualifications of individuals involved in clinical investigations
- Procedures for appeals of decisions made about clinical investigations

Further details of the role of national research ethics committees in the context of clinical investigations for medical devices are also set out in a separate statutory instrument, the European Union (National Research Ethics Committee for Clinical Investigations of Medical Devices) Regulations 2021 (S.I. No. 260 of 2021).

- S.I. No. 314 - 2018 Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018 (Amended In 2019 And 2021).
- The Guidance on Retrospective Chart Review Amendment to the HRR January 2021 details the conditions that consent will not be required for low-risk retrospective chart reviews that meet specified transparency requirements and are approved by a research ethics committee. A 'retrospective chart review study' means: a low-risk research study carried out by a controller (a controller can be a hospital, GP practice etc.) on personal data only, where that controller has already obtained that personal data.

Declaration of Helsinki

- The Declaration of Helsinki is a set of ethical principles regarding human experimentation developed in 1964 for the medical community by the World Medical Association (WMA).
- It is cited in most national or international guidelines and clinical investigation protocols.

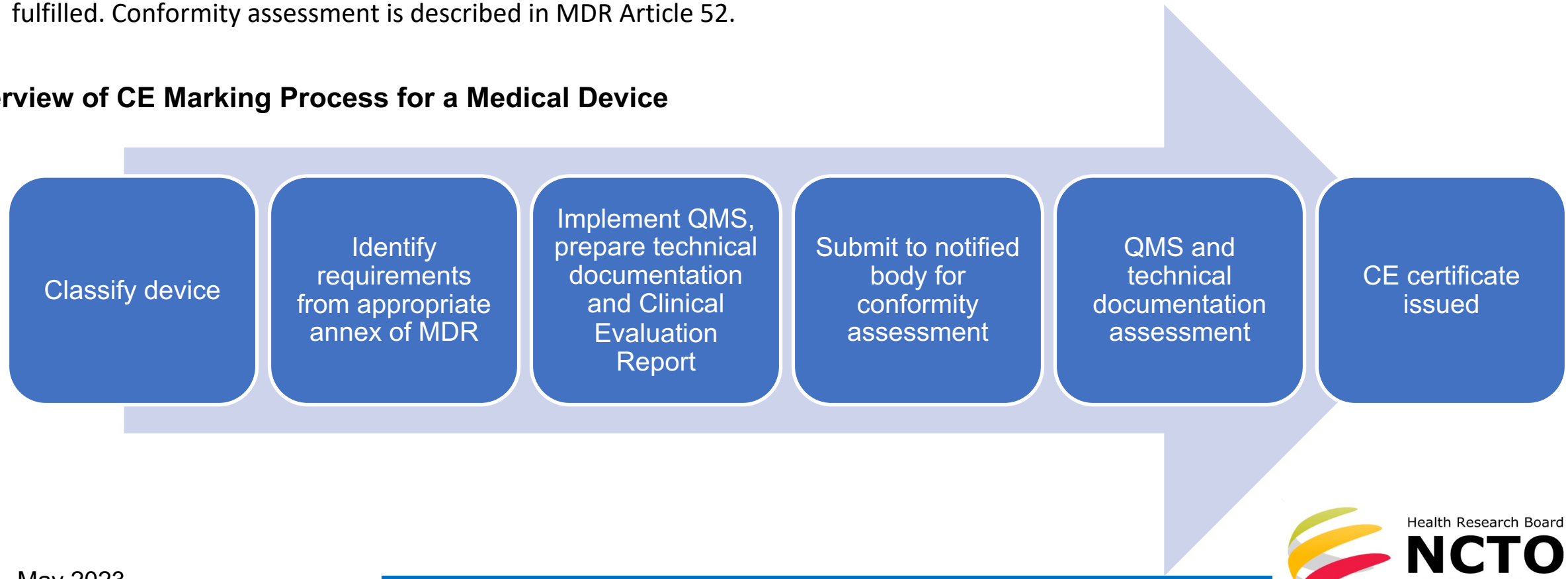
Some of the basic principles in the declaration include:

- The "***well-being of the human subject should take precedence over the interests of science and society***."
- Informed consent should be recorded in writing.
- Limits the use of Placebo
- "**Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results**."

European Market Access (CE Marking)

- Market access is granted by a declaration of conformity verified by a certificate issued by a notified body - CE (Conformite Europeene) mark.
- Conformity assessment is the process of demonstrating whether the requirements of the MDR relating to a device have been fulfilled. Conformity assessment is described in MDR Article 52.

Overview of CE Marking Process for a Medical Device



Post-Market Clinical Follow Up (PMCF)

- The MDR considers post-market clinical follow-up (PMCF) as an ongoing process.
- MDR part B of Annex XIV includes a set of requirements for developing a plan necessary to implement PMCF.
- The PMCF plan shall be part of the post-market surveillance plan.
- The PMCF evaluation report shall be part of the clinical evaluation report.

Post-market Clinical Follow-up template MDCG 2020-7

References	Title
Part B Annex XIV	Post-market Clinical Follow-up
Article 29	Registration of Devices
Article 30	Electronic system for registration of economic operators

US Approval (FDA)

FDA's Center for Devices and Radiological Health (CDRH) regulates firms that manufacture, repackage, relabel and import medical devices sold in the United States.

Classification of Medical Devices: Medical devices are classified into Class I, II, and III in the US. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval (PMA).

Regulatory Pathways

- **Premarket Notification 510(k)** - A 510(k) must demonstrate that a device is substantially equivalent to a device legally in commercial distribution in the United States.
- **Premarket Approval (PMA)** - Products requiring PMAs are Class III devices (high-risk devices that pose a significant risk of illness or injury). The PMA process is more involved and requires extensive clinical data to support claims made for the device.
- **De Novo** – A marketing pathway to classify novel medical devices for which no legally marketed predicate device exists. De Novo classification is a risk-based classification process of class I and II devices.

Clinical Investigations in the US (FDA)

Clinical Investigations

- **Investigational Device Exemption (IDE)** - allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a PMA application or 510(k) submission to FDA.

- **Nonsignificant risk studies (NSR)** - Studies with devices of nonsignificant risk. Before they begin, these studies must be approved by the IRB only (not the FDA).

- **Early Feasibility Study (EFS)** - A limited clinical investigation of a device early in development. They typically enrol a small number of subjects. An EFS evaluates the device design concept concerning initial clinical safety and device functionality and may guide device modifications.

Clinical Investigations in the US (FDA)

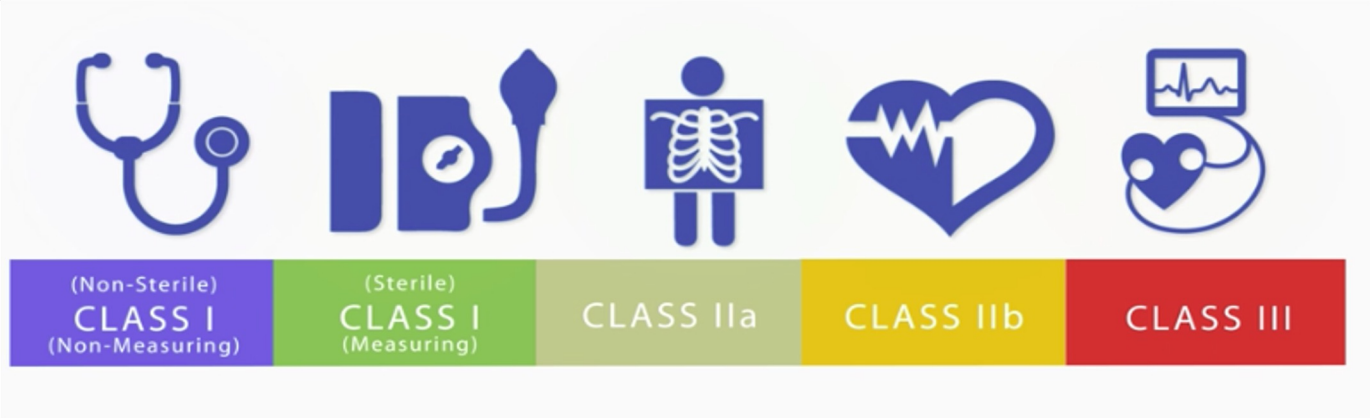
Investigational Device Exemption (IDE) Study Execution regulations

- Protection of Human Subjects, Informed Consent - 21 CFR 50
- Financial Disclosure of Investigators - 21 CFR 54
- Institutional Review Boards - 21 CFR 56
- Sponsor, Monitor, Investigator Obligations - 21 CFR 812 Subparts C, D, E (device) and CFR 312 Subpart D (drug) combination product

FDA **Medical Device Databases links**

- **CFR Title 21 – Food and Drugs**
- **510(k) Premarket Notification**
- **Premarket Approvals (PMAs)**
- **De Novo Classification Orders**
- **MAUDE** data represents reports of adverse events involving medical devices.

Medical Device Classification in Europe



Classification of Medical Devices (EU)

- The classification of medical devices is a risk-based system considering the “vulnerability of the human body and the potential risks associated with the devices”.
- The higher the class of the device, the greater the involvement of a notified body in conformity assessment.
- The ‘classification rules’ are described in Article 51 and set out in Annex VIII of the MDR.
- The guidance (MDCG_2021-24) provides a general overview of the classification of medical devices, presents definitions and terms that help carry out classification and details the rules, providing examples.
- In December 2022, a manual on borderline and classification for medical devices was updated to record the agreements concerning the borderline between medical devices and other products.

General Data Protection Regulation (GDPR)

The General Data Protection Regulation (GDPR) is a privacy and security law. It was drafted and passed by the European Union (EU), but imposes obligations onto organizations anywhere, so long as they target or collect data related to people in the EU.

General Data Protection Regulation (GDPR)

- EU General Data Protection Regulation (GDPR) was enacted in May 2016 and came into legal effect on 25 May 2018
- Key regulatory points of the GDPR:
  - **Data protection principles** - If you process data, you must follow the protection and accountability principles outlined in **Article 5.1-2**. For Example, You should collect and process only as much data as necessary.
  - **Accountability –** You must be able to demonstrate you are GDPR compliant. This involves documenting team responsibilities, data you gather, training and agreement contracts.
  - **Data Security –** You must implement appropriate technical and organisational measures to protect data.
  - **Instances in which it's legal to process personal data** are listed in **Article 6**. For example, if you receive consent from a data subject.
  - **Data Subjects' Privacy Rights** include the rights to be informed, of access, to rectify, to raise, to restrict processing, to object, to data portability and concerning automated decision-making and profile**.**

Resource: https://gdpr.eu/what-is-gdpr/

Data Protection Impact Assessments (DPIA)

- The HRB has prepared GDPR guidance for researchers. This website details links to HSE guidance documents and FAQs.
- GDPR introduces **Data Protection Impact Assessments (DPIA)** that manage the risks of processing personal data, including for a clinical investigation. DPIAs are required when the processing is *"likely to result in a high risk to the rights and freedoms of natural persons"* (Article 35(1)).
    - European Commission - Guidelines on DPIA and determining whether processing is "likely to result in a high risk" for Regulation 2016/679
    - Data Protection Commission (Ireland) – Guide to Data Protection Impact Assessments (DPIA)

Data Protection and Informed Consent in Health Research

- The **Health Research Data Protection Network (HRDPN),** a Network of Universities, the HSE, Hospitals, NCTO, and not-for-profit Research Organisations/Networks, developed the HRDPN Practical Guide On Data Protection For Health Researchers.
- Rules are set by the Data Protection Health Research Regulations 2018 (S.I. No. 314 - amended in 2019 and 2021).
  - The regulations require "assessment of data protection implications of the health research" or (if high risks to individuals) a DPIA.
- The HSE have prepared material, including the DPIA workshop presentation and website - Data Protection and Research in Health and Social Care.
- The HRB website details what information needs to be provided to researchers for informed consent - 'Guidance on information principles for informed consent for the processing of personal data for health research'.

Good Clinical Practice

ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects.

A standard for clinical research professionals during the design, conduct, recording, and reporting of clinical investigations related to the safety and performance or effectiveness of medical devices (in-vitro diagnostic medical devices are excluded from the scope of the standard).

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ISO 14155:2020

- Applies to "***design, conduct, recording and reporting***" of medical device clinical investigations for pre- and post-market investigations.
- Aims to protect subjects, ensure data integrity
- Defines sponsors' investigators', and Ethics Committees/ Investigational Review Boards' responsibilities.
- Used for regulatory compliance in Europe and globally. The FDA recognises ISO 14155 and accepts clinical data collected outside the U.S. when the standard is followed.
- In 2020, the standard was updated to harmonise with global GCP guidelines and consider requirements associated with new technologies (such as electronic consent, e-signatures and data privacy). In addition, the new standard addresses quality by design and risk-based monitoring.
- Clause 5, "Ethical Principles", addresses the influence and compensation of subjects, database registration, responsibilities, interactions with ethics committees, vulnerable populations and informed consent.

ISO 14155:2020

- Clause 6, **“Clinical Investigation Planning”,** details the documentation requirements and roles of the personnel involved. An individual with relevant medical expertise and experience must be accessible to the sponsor.
- Clause 7, **“Clinical Investigation Conduct”,** details the practices required to ensure strict accountability and tight controls over documentation and recording during the investigation.
- Clause 8, **“Closing out a Clinical Investigation”,** addresses reporting and retention associated with terminated, suspended or routinely closed out clinical investigations.
- Clause 9 and Clause 10, **“Responsibilities of the Sponsor and Principal Investigator”** (respectively)
- The Annexes detail what needs to be included in the **clinical investigation plan, investigator’s brochure, case report forms, clinical investigation report** and other essential documents.

Medical devices — Quality Management Systems (QMS) — ISO13485:2016 Requirements for Regulatory Purposes

An internationally agreed standard that sets out the requirements for a quality management system.

The standard in intended for groups that are involved in the "design, production, installation and servicing" of medical devices.

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ISO 13485:2016

- Quality management systems (QMS) are a set of policies, processes and procedures for medical device development required by regulators. ISO 13485 can help organisations involved in any part of a medical device's life cycle.

Certification to ISO 13485

- Certification aims to demonstrate that you have met the requirements of the standard.
- It is possible to implement the standard without undergoing the certification process.
- Third-party certification is required by regulators for market access in Europe.
- Notified Bodies are assigned to audit medical device companies for compliance with ISO 13485.

The standard covers a number of topics including:

- **General requirements** include quality manual content, medical device files, control of documents and control of records (part 4).
- **Management responsibilities** include customer focus, quality policies, planning, authority, communication and reviews by management (part 5).
- **Resource management** includes human resources, infrastructure and controlled work environments (part 6).
- **Product realisation** includes design development planning, user requirements, design controls, purchasing and supplier control (part 7).
- **Measurements, analysis and improvement** include complaint handling, internal audit process and product monitoring, nonconformances and CAPAs (part 8)

ISO 13485:2016 (Design Validation)

- ISO 13485 requires that as part of design and development validation, the organization perform clinical evaluations or performance evaluations of the medical device.
- Design and development validation is focused on proving that the device meets its specified intended use.

ISO 13485 details requirements for design validation including:

- A validation plan that includes methods, acceptance criteria, and, as appropriate, statistical techniques with rationale for sample size.
- Use of representative product.
- Records of the results and conclusion of validation.
- Objective of the test
- Test methods and procedures (including any specific test conditions)
- Study endpoints (usually both safety and effectiveness)
- Statistical methodology used
- Study results, analyses performed (including statistical, as appropriate), and conclusions

Risk Management

ISO 14971:2019— Application of risk management to medical devices.

A standard for medical device manufacturers describing the terminology, principles and a process for risk management of medical devices including software as a medical device and in vitro diagnostic medical devices.

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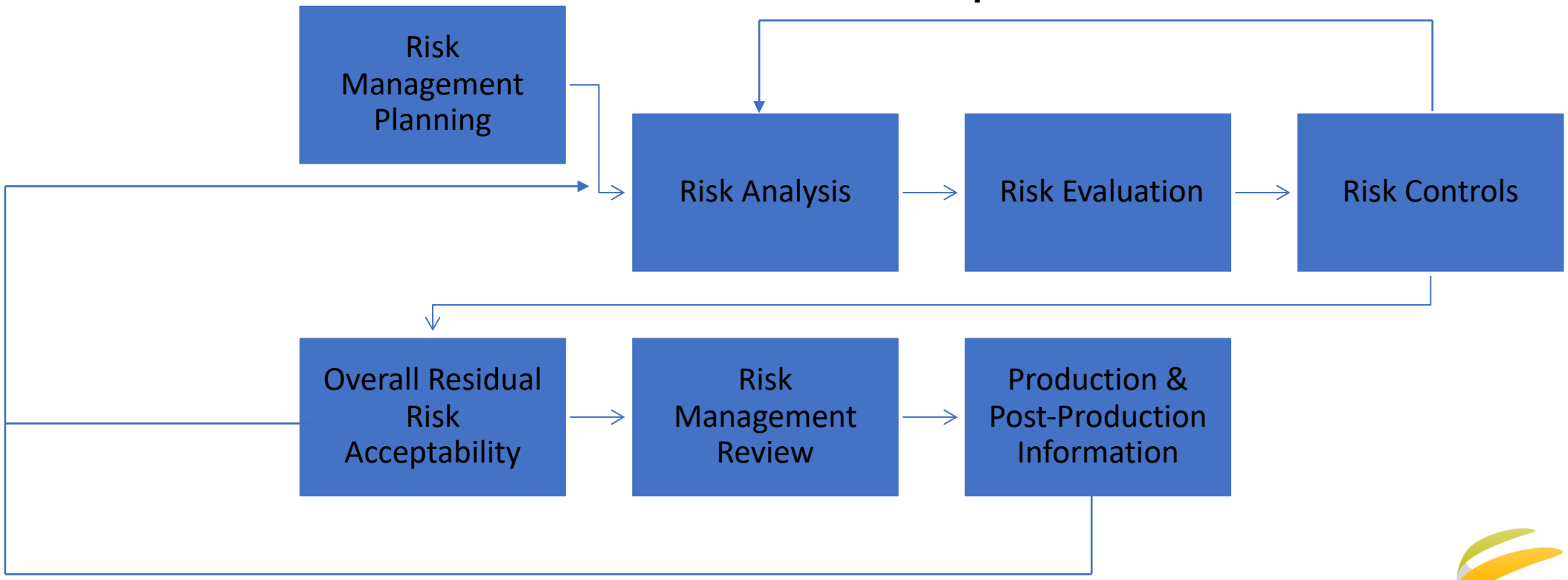
ISO 14971:2019

- The objective of medical device risk management is to identify the hazards associated with the medical device, estimate and evaluate the associated risks, control these risks, and monitor the effectiveness of the controls.

A Schematic Representation of the Risk Management Process for Medical Device Development



Application of ISO 14971:2019 to Clinical Investigations

- The "**Application of ISO 14971 to clinical investigations**" (Annex H of ISO 14155) was introduced in 2019. Figure H.1 details a **flow chart of the inter-relationship between device risk management (ISO 14971) and the clinical investigation process (ISO 14155).**
- The product's residual risk(s), as identified in the risk analysis (ISO 14971), along with the patient risks relating to the clinical procedure (ISO 14155), must be balanced against the anticipated patient benefits.
- The Clinical investigation plan, IFU, Investigator's Brochure and informed consent form must include a summary of the residual risks. These residual risks are considered anticipated adverse device effects.
- Where risk mitigation requires training on the device, the extent of the training support by the sponsor should be considered.

Clinical Evaluation

IMDRF: 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 device when used as intended by the manufacturer.

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Clinical Evaluation

- Clinical evaluation is part of the QMS and is based on analysing available pre- and post-market clinical data relevant to the device's intended purpose.
- **The clinical evaluation report (CER)** includes all the relevant clinical data documented or referenced in other parts of the technical documentation. This will be part of the conformity assessment for the device.
- **The notified body uses a clinical evaluation assessment report (CEAR)** to assess the clinical evidence presented in the CER. Clinical Evaluation Assessment Report Template MDCG 2020-13 details the evaluation criteria.

References	Title
MEDDEV 2.7/1 revision 4	Guidelines on medical devices, clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC
MDR, Article 61	Clinical evaluation
MDR Section 4 of Annex XIV Part A.	Clinical Evaluation and Post-market Clinical Follow-up Part A Clinical Evaluation

Clinical Evaluation – Equivalence

- If clinical data for an **equivalent** device is available, it may be justified that a clinical investigation is not required as part of the clinical evaluation.
- The guidance MDCG_2020 -5 does state that carrying out a clinical investigation is the most direct way to generate clinical data for CE marking. However, it allows for **sourcing clinical data from the literature** (for example) for a device where equivalence can be demonstrated to the device in question.
- It has been recognised that some of the requirements set out in MEDDEV 2.7/1 rev. 4 need to be fully aligned with the MDR. Therefore, in cases of divergence between the MEDDEV 2.7/1 rev. 4, this MDCG guidance and the MDR, the MDR shall take precedence.

References	Title
MEDDEV 2.7/1 revision 4	Guidelines on medical devices, clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC
MDR, Article 61	Clinical evaluation
MDR Annex XIV Part A.	Clinical Evaluation and Post-market Clinical Follow-up Part A Clinical Evaluation

Medical Device Software (MDSW)

Means Software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a "medical device" in the Medical Devices Regulation (MDR) or In Vitro Diagnostic Medical Devices Regulation (IVDR).

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Qualification and Classification of Software

- **MDSW is software with an intended purpose and independent clinical benefit that can be used independently or in conjunction with a medical device.** Software used with medical devices without independent clinical benefit is not MDSW but is considered an accessory or component of the medical device.
- The guidance MDCG 2019-11 provides examples of software that are medical devices (e.g. diagnostic software that supports clinical decisions) and those that are generally not (e.g. electronic patient record and data management systems).
- For example, Software that processes, analyses, creates or modifies medical information may or may not be qualified as medical device software. If there is a medical intended purpose, e.g., the processed data supports diagnosis, or the modified image serves as a decision support, it is considered MDSW. However, altering data for embellishment/cosmetic or compatibility purposes does not qualify the software as MDSW.

Clinical Evaluation (MDR) / Performance Evaluation (IVDR) Of Medical Device Software

- The guidance MDCG 2020-1 will help determine the appropriate level of clinical evidence required for Medical Device Software (MDSW) and details the following stages required to generate clinical evidence.

    1. **Valid clinical association (MDR) and scientific validity (IVDR)** of software. This involves justifying the association of an MDSW output (e.g. abnormal cardiac sounds from a digital stethoscope) with a clinical condition or physiological state (e.g. heart arrhythmia).
    2. **Technical / Analytical Performance –** Involves using objective evidence to show that the MDSW specifications conform to user needs and intended uses and that the requirements can be consistently fulfilled through testing (Verification & Validation)
    3. **Clinical Performance –** involves proving the ability of the MDSW to achieve its intended purpose leading to a clinical benefit.
    4. **Compilation of Clinical Evidence –** Preparation of the Clinical Evaluation Report.

- IMDRF/SaMD WG/N41 - Software as a Medical Device (SaMD): Clinical Evaluation, 2017

Cyber Security and Data Protection

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Cybersecurity for Medical Devices

- The MDR enhances the focus on cybersecurity risks and outlines new safety requirements in Annex 1 for electronic programmable systems and software.
- Manufacturers must address information (data) security, IT (computer system) security and Operation (procedures and workflows) security of their devices. Reference Figure 1 of MDCG 2019-16 (on the next slide).
- It is not just the manufacturer that is responsible for cybersecurity. It is recommended that the manufacturer establish agreements to ensure that all parties understand the joint responsibility.
- The MDR and MDCG do not explicitly detail requirements subject to other legislation (such as Cybersecurity Act, GDPR, DPIA and NIS) associated with cybersecurity, privacy and confidentiality.

Figure 1 from MDCG 2019-16

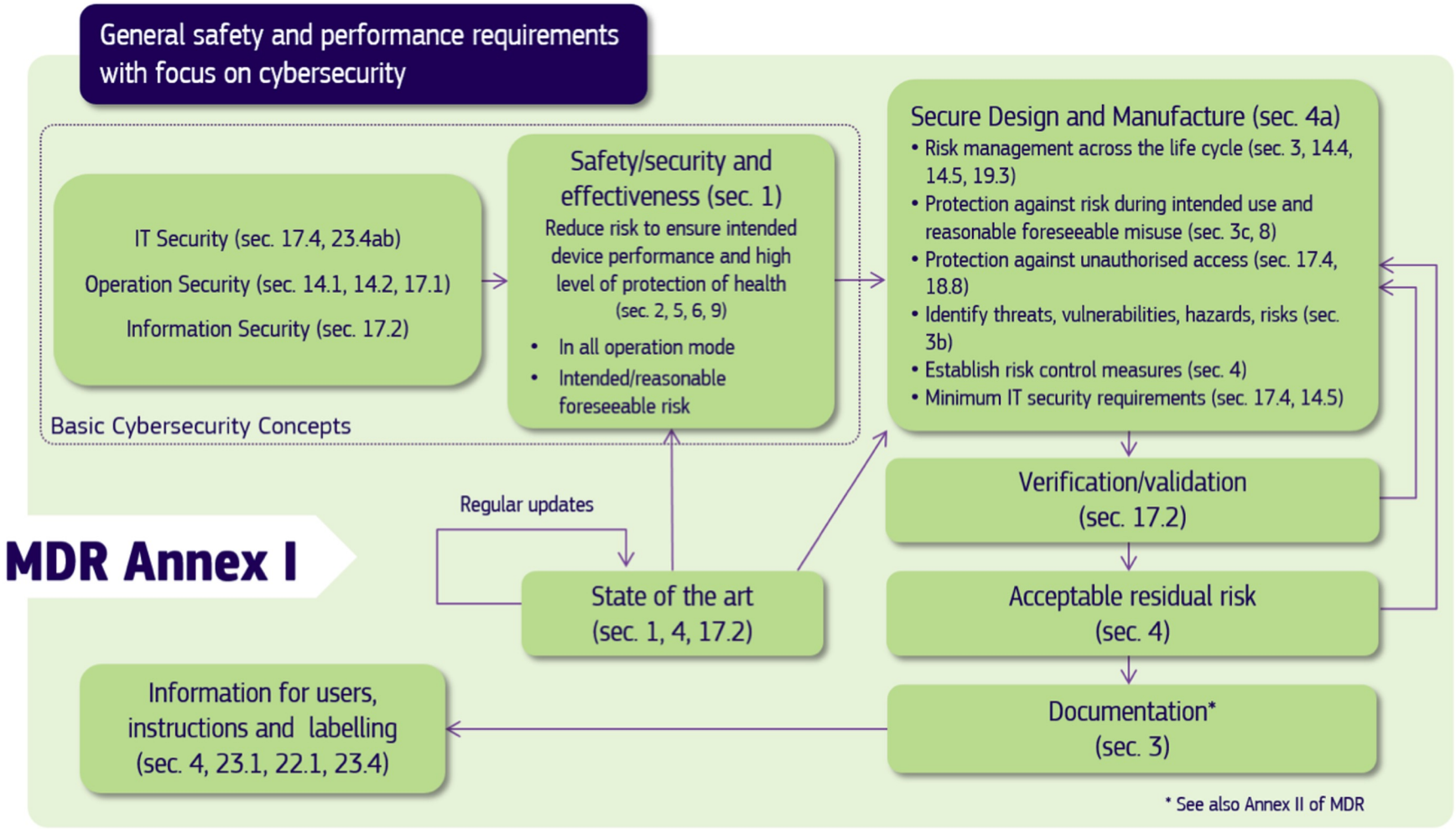

Figure 1: Cybersecurity requirements contained in MDR Annex I

Some useful definitions from the MDR

‘active device’ means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices. Software shall also be deemed to be an active device;

‘conformity assessment’ means the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled;

‘conformity assessment body’ means a body that performs third-party conformity assessment activities including calibration, testing, certification and inspection;

‘notified body’ means a conformity assessment body designated in accordance with this Regulation;

‘invasive device’ means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body;

‘Common Specifications’ a set of technical and/or clinical requirements, other than a standard, that provides a means of complying with the legal obligations applicable to a device, process or system.

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Additional information

Health Research Board
NCTO
National Clinical Trials Office

Guidance on the health institution exemption under Article 5(5) MDCG 2023-1 (In-house devices)

- An in-house device is a medical device manufactured and used only within EU health institutions on a non-industrial scale to address the specific needs of target patient groups which cannot be met by an equivalent CE-marked device available on the market.
- In-house medical devices can be exempted from most MDR requirements (except annex 1), provided the health institution meets the conditions detailed in Article 5(5) of the MDR.
- The device must be manufactured and used within the same health institution and cannot be transferred to another legal entity.
- Wearables and other devices used on patients outside the institution are not ‘in-house.’

Health Research Board
NCTO
National Clinical Trials Office

Guidance on sampling of devices for the assessment of the technical documentation MDCG_2019-13

- MDR outlines requirements for sampling higher-risk devices before issuing a QMS cert.
- The notified body must draw up a sampling plan (per Section 4.5.2(a) of Annex VII) that will detail the devices, the (planned) assessment dates and the status of these assessments of technical documentation that will continue after the certificate is issued.

References	Title
Annex VII (Section 4.5.2(a))	Requirements to be Met by Notified Bodies
Annex IX (Section 2.3)	Conformity Assessment Based on a Quality Management System and on Assessment of Technical Documentation

Guidance on safety reporting in clinical investigations of medical devices MDCG_2020-10

- The MDR requires that the sponsor report, without delay, all the following using the electronic system (Article 73):
  - any serious adverse event
  - any device deficiency that might have led to a serious adverse event
  - any new findings about any event referred to in points a) and b).
  - The period for reporting shall take into account the severity of the event.

MDR reference	Title
Article 80	Recording and reporting of adverse events that occur during clinical investigations
MDR chapter VII	Post-market Surveillance, Vigilance and Market Surveillance

Summary of safety and clinical performance MDCG 2019-9

- The MDR requires a **summary of safety and clinical performance** (SSCP) for implantable and class III devices.
- The SSCP will be made available to the public AND is intended to provide public access to an updated summary of clinical data and other information about the safety and clinical performance of the medical device.
- The primary purpose of the MDCG guidance is to guide the presentation, content and validation of the SSCP.

MDR reference	Title
Article 32	Summary of safety and clinical performance
Article 18	Implant card and information to be supplied to the patient with an implanted device

Guidance on harmonised administrative practices and alternative technical solutions until EUDAMED is fully functional and Instructions for generating CIV-ID for MDR Clinical Investigations

- Article 33 of Regulation (EU) 2017/745 on medical devices (MDR) requires the Commission set up a European database on medical devices ('EUDAMED').
- EUDAMED will comprise six electronic systems (so-called 'modules') which facilitate the collation and processing of information. Modules include registration of relevant economic operators (actor registration), devices and systems and procedure packs (UDI), notified bodies & certificates, certain aspects of conformity assessment, clinical investigations, vigilance and market surveillance and post-market surveillance.
- For a clinical investigation, in the absence of EUDAMED, the unique single identification number, which shall be used for all relevant communication about that clinical investigation, will be the CIV-ID and will be set up by the competent authority.
- The guidance provides step-by-step instructions with screenshots that cover the generation of a CIV-ID for MDR clinical investigations in Eudamed.

Clinical evaluation consultation procedure exemptions Interpretation of article 54(2)b MDCG_2019-3

- Criteria for exemption from pre-market clinical evaluation 54(2):

  a) **Renewal of a certificate**

  b) **Modified devices -** where the device has been designed by modifying a device **already marketed** by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device; or

  c) **Compliance with a Common Specification**

- This guidance document aims to clarify 54(b) - modified devices,
  - The word “marketed” is used, but it is unclear if it means marketed under old directives (MDD) or existing regulations (MDR).
- The guidance concludes that devices marketed under the directive and MDR are applicable.
- As part of its technical documentation assessment according to the MDR, the notified body will verify that the “modifications”, as referred to in the main document, do not adversely affect the benefit-risk ratio.