

Medical Device Regulation: Impact on clinical evidence requirements

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Comparative Market Information

- ▶ Estimated global market size (Revenue)
 - **Pharmaceuticals**
 - US\$1,205 billion in 2018 (Source: Statistica.com)
 - **Medical Devices**
 - US\$477 billion by 2020 (Source: futurebusinessinterests.com)
 - **IVD**
 - US\$69 billion (Source: grandviewresearch.com)
- ▶ Western Europe is more than 25% global market share led by DE, FR, UK, ITA
- ▶ The sector represents some 25 000 companies, of which 95% are Small and Medium-sized Enterprises (SMEs)

Pharmaceutical v's Device

Pharmaceutical & Biologic Product	Medical Device/Diagnostic/Technology
Traditionally based on pharmacology and chemistry.	Traditionally based on mechanical, electrical and materials
Product developed by trial on substance selected due to it's efficacy and safety.	Product engineered to perform a function (specific and safely). Effect may be patient triggered or adaptable to condition.
Effective when absorbed into body. Pharmacologically active.	Effective by electrical/mechanical action. Pharmacologically inactive.
Continuous but not rapid innovation, long term evaluations to determine effects and side effects.	Continuous and rapid innovation based on new science, technology and materials.
Extensive product life cycle – initially 'prescription only' moving to OTC. Allows for longer amortization period.	Short product life cycle due to continuous incremental improvements, often user related and driven. Short amortization period.

Applicable Standards

- ▶ **BS EN ISO 13485**

Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes

- ▶ **BS EN ISO 14971**

Medical Devices - Application of risk management to medical devices

- ▶ **ISO 10993**

Biological Evaluation of medical devices

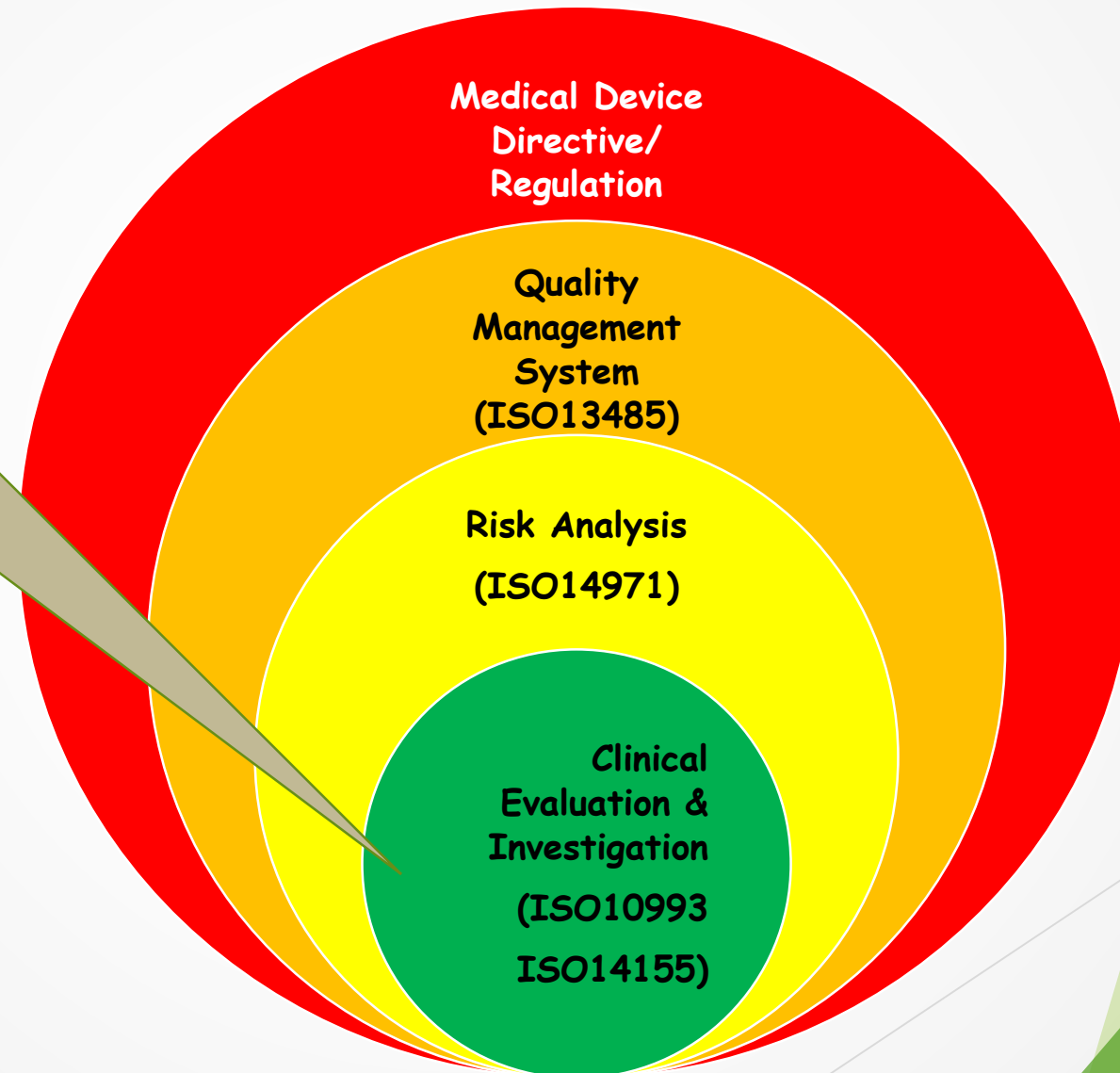
- ▶ **BS EN 62366**

Medical Devices - Application of usability engineering to medical devices

- ▶ **BS EN ISO14155**

Clinical Investigations of medical devices for human subjects - Good Clinical Practice

Completion of General Requirements for Compliance with MDD/MDR & Declaration of Conformity to Obtain CE Mark



Key Processes

- ▶ QMS System
 - ▶ Accreditation to ISO13485 Standard
 - ▶ Risk Analysis to ISO14971 Standard
 - ▶ Framework for Regulatory Approval
- ▶ Controls the Overall Process
 - ▶ Concept & Voice of Customer (Design Inputs)
 - ▶ Feasibility Evaluation (Design Outputs)
 - ▶ Risk Analysis to identify problems and gaps in knowledge
 - ▶ Quality control of Preclinical testing
 - ▶ Quality control of Clinical Assessments
 - ▶ Design Verification and Validation
 - ▶ Quality Documentation for Submission

Key Processes

- ▶ Clinical Evaluation Report (CER)
- ▶ Clinical Development Plan
 - ▶ Preclinical Testing based on ISO10993 & Specific ASTM/ISO standards related to implant concerned
 - ▶ Biomechanical, Biological, Physico-chemical Characterisation
 - ▶ Labelling, packaging, sterility
 - ▶ Specifics for Active Devices such as Electrical, Software
 - ▶ Clinical Investigations based on ISO14155 (GCP Equivalent)
 - ▶ Pre Market
 - ▶ Post Market



CE

MEDDEV 2.7/1 Rev 4

Clinical Evaluation - A Guide for Manufacturers and Notified Bodies

Definition of clinical evaluation

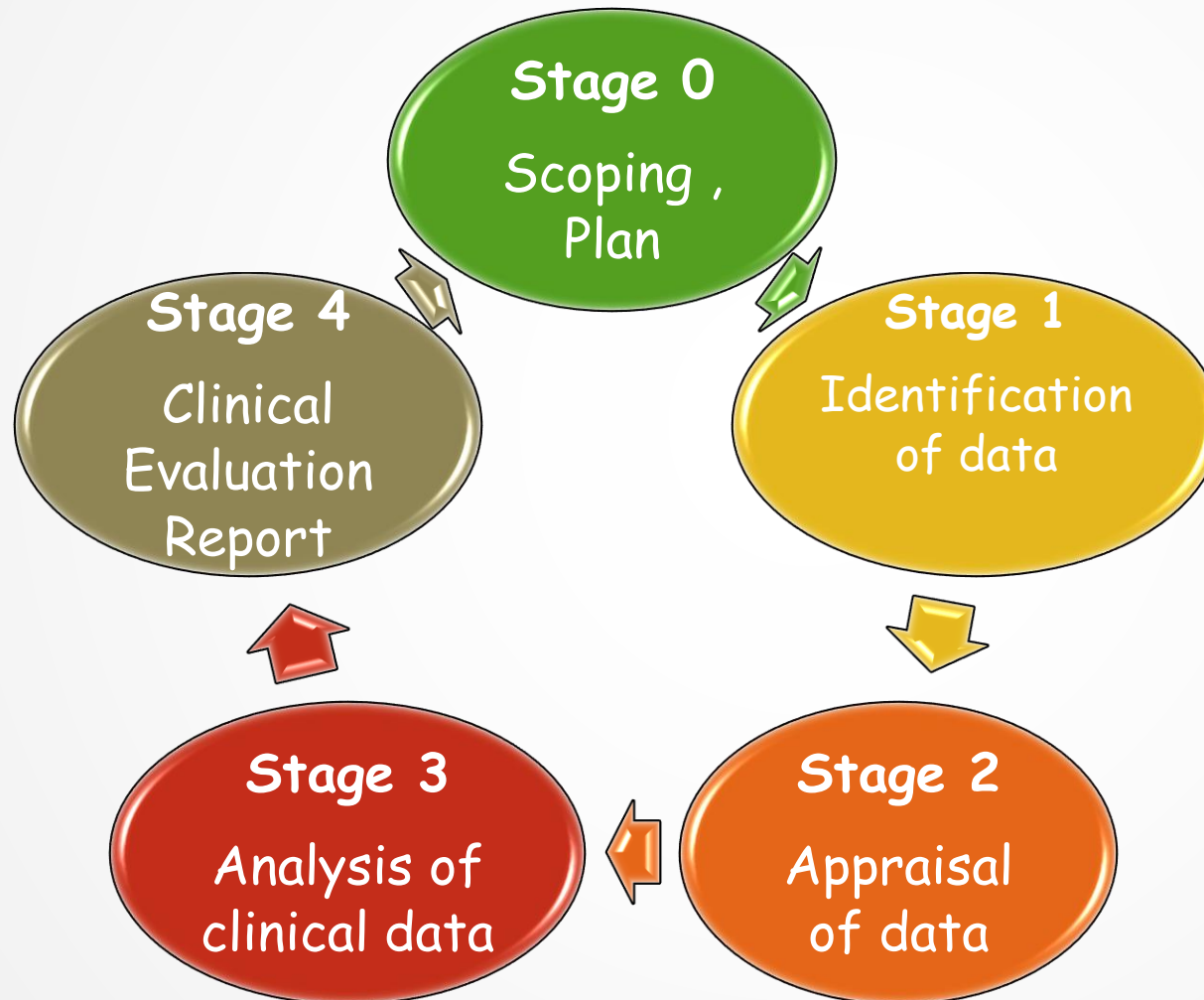
Clinical evaluation:

- ▶ “A methodologically sound ongoing procedure to collect, appraise and analyse **clinical data** pertaining to a medical device and to evaluate whether there is sufficient **clinical evidence** to confirm compliance with relevant essential requirements for **safety and performance** when using the device according to the manufacturer's Instructions for Use”.
- ▶ The MEDDEV guidance is not legally binding. However, Notified Bodies use it as a reference.

Clinical data should be sourced from:

- clinical investigation(s) of the device concerned; or
- clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which **equivalence** to the device in question can be demonstrated; or
- published and/or unpublished reports on other clinical experience of either the device in question or an **equivalent** device.

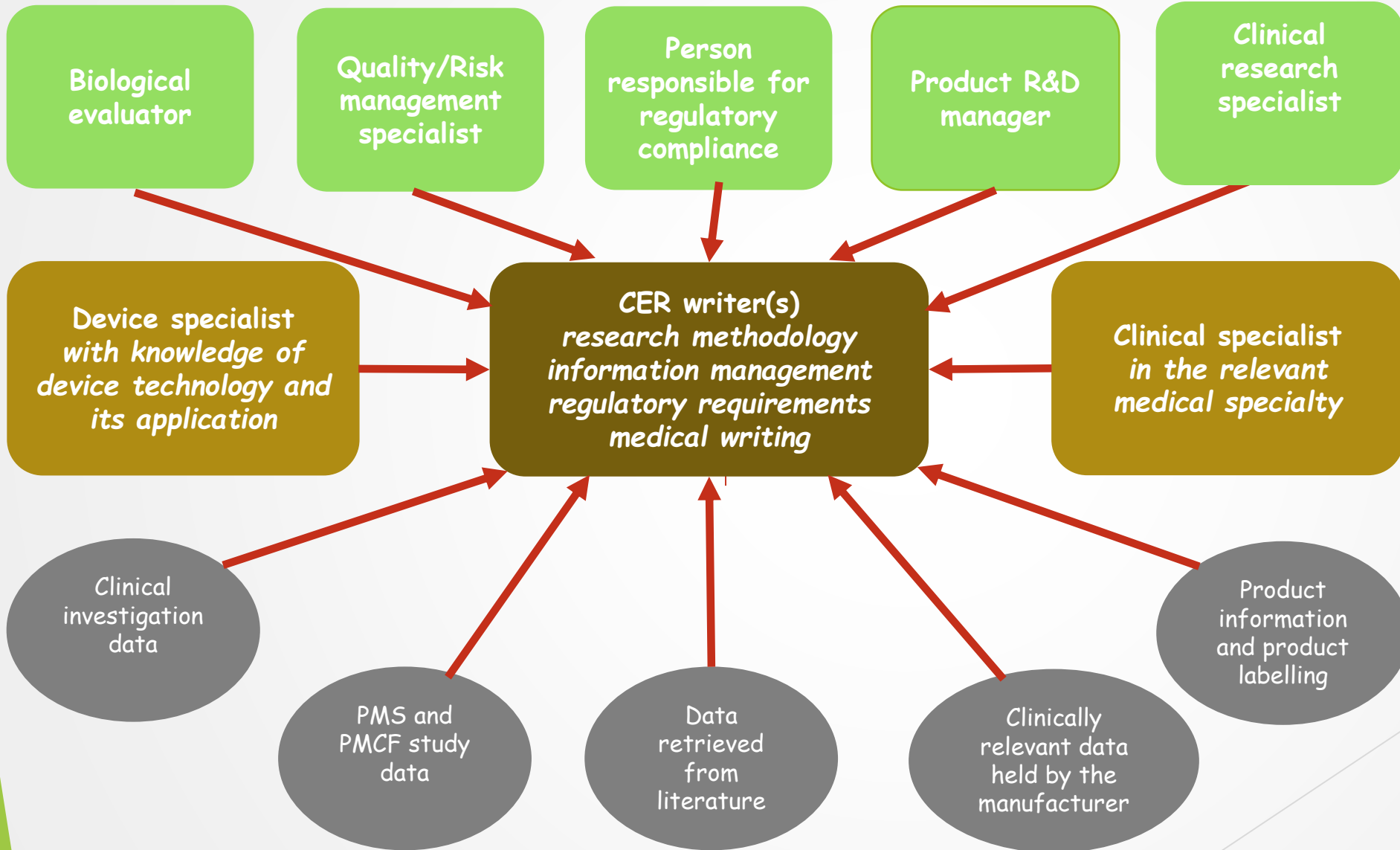
Clinical Evaluation Process



Major components of the CER

- **Scope and Clinical Evaluation Plan**
- **State of the Art**
 - *Clinical data used to demonstrate conformity need to be in line with current knowledge/the state of the art*
 - *Data on the safety and performance of other devices and alternative therapies should be used to define the state of the art.*
- **Literature Search**
- **Device Description**
- **Device Equivalency**
- **Analysis of clinical data** - has to satisfy essential requirements on:
 - *safety*
 - *performance*
 - *acceptable benefit/risk profile*
 - *acceptability of side-effects*
- **Conclusions**

A TYPICAL CLINICAL EVALUATION



Clinical Investigations

AND PMCF STUDIES

Types of devices requiring clinical investigation data

- ▶ Most likely to require clinical investigation data:
 - implants and high-risk devices
 - devices based on technologies where there is little or no experience
 - devices that extend the intended purpose of an existing technology (i.e. a new clinical use)
 - ▶ Clinical investigation data may also be required for:
 - class I devices
 - class IIa devices
 - class IIb devices that are not implantable
- "because the need for clinical investigations depends on the ability of the existing data to adequately address the benefit/risk profile, claims, and side-effects"

Decisions about clinical investigations

- MEDDEV 2.7/1 Rev 4 acknowledges that the decision to conduct a clinical investigation is a difficult and important one. It should be made as early as possible and based on rational, scientific grounds.
- “As the initial clinical evaluation identifies the questions to be answered by a clinical investigation, the clinical evaluation process should generally commence **in advance of any clinical investigation.**”
- It is acknowledged that randomized clinical investigations may not always be feasible and/or appropriate and the use of alternative study designs may provide relevant clinical information.

Clinical investigations: standard and guidance

- ▶ The Medical Device Directive only has a single article on the subject of clinical investigations.
- ▶ **ISO14155: 2011** (International Standard Clinical Investigation of Medical Devices for Human Subjects - *Good Clinical Practice*):
 - ISO 14155 specifies requirements to ensure that the clinical investigation establishes the medical device's performance by mimicking normal clinical use.
- ▶ **MEDDEV 2.7/4 Guidelines on clinical investigation**
- ▶ When must/should a clinical investigation be undertaken?
 - for active implantable medical devices as well as for class III and implantable medical devices - unless it is duly justified to rely on existing data. Any such justification will have to be based on a proper clinical evaluation.
 - Depending on clinical claims, risk management outcome and on the results of the clinical evaluation, clinical investigations may also have to be performed for nonimplantable medical devices of classes I, IIa and IIb.

What does ISO14155 cover?

In Europe ISO14155 supports the Medical Device Directive and the Active Implantable Medical Device Directive (nb: It does NOT apply to In Vitro Diagnostic Medical Devices)

It contains:

- ▶ **9 Sections**

- ▶ Scope, Normative References, Terms & Definitions, Ethical Considerations, CI planning, CI Conduct, Suspension/Termination/Close-out, Responsibilities Sponsor, Responsibilities PI

- ▶ **6 Annexes**

- ▶ Clinical Investigation Plan (N), Investigators Brochure (N), Case Report Form (I), Clinical Investigation Report (I), Essential Clinical investigation Documents (I), Adverse Event Categorisation (I)

Normative references are necessary for the application of the standard in which they are mentioned (they shall be publicly available and in English).

Informative references assist the user with regard to a particular subject area.

When should ISO14155 be applied?

Clinical Investigations carried out in human subjects to assess the **SAFETY** and **PERFORMANCE** of medical devices for **REGULATORY PURPOSES**

Principles set forth should be applied to **ALL** other clinical investigations, and should be followed as far as possible, considering the nature of the clinical investigation and the requirements of national regulations.

The Future: ISO14155 2020

ISO14155 is currently being updated, main changes include:

- ▶ Inclusion of a summary section of *GCP* principles
- ▶ Reference to registration of clinical investigation in publically accessible database
- ▶ Guidance with regards clinical quality management
- ▶ Inclusion of risk based monitoring
- ▶ Guidance on statistical considerations
- ▶ Guidance **for** Ethics Committees
- ▶ Reinforcement of risk management throughout process of clinical investigation
- ▶ Clarification of applicability of the Standard to different clinical development stages
- ▶ Inclusion of guidance on clinical investigation audits

MEDDEV 2.12/2 Rev 2: Guidelines on PMCF studies

- ▶ There are often limitations to clinical data collected during the premarket phase, due to:
 - The limited number of subjects and investigators
 - The relative heterogeneity of subjects and investigators
 - Controlled setting unlike the full range of clinical conditions in general medical practice
- ▶ PMCF study: “a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labelling”
 - The data and conclusions derived from the PMCF study are used to **provide clinical evidence for the clinical evaluation process**.
- ▶ PMCF studies can follow several methodologies, for example:
 - the extended follow-up of patients enrolled in premarket investigations
 - a new clinical investigation
 - a review of data derived from a device registry
 - a review of relevant retrospective data from patients previously exposed to the device

Medical Device Regulation (MDR)



MDR 2017/745

- Entered into force on May 26, 2017. Date of Application will be May 26, 2020.
- Regulations have binding legal force throughout every Member State, on a par with national laws.
- All devices currently on the market will need to be re-evaluated and certified under MDR.
- Certificates issued under current directives after 26 May 2017 will be valid for max 5 years, but will become void at latest 4 years after Date of Application.

MDR ChpVI: Clinical Evaluation & Clinical Investigation

- Increased focus on clinical evaluation and clinical investigation
- Inclusion of MEDDEV 2.7.1 and parts of ISO14155
- Art 62 - 82 concerned with clinical investigations
- Manufacturer may request clinical strategy review from Expert panel
- EUDAMED - to include clinical investigation data & PMCF
- Clinical investigation documentation detailed precisely (Art 74)

MDR: Definitions

Clinical evaluation

- ▶ “a systematic and planned process to continuously generate, collect, analyse and assess the **clinical data** pertaining to a device in order to verify the safety and performance, including **clinical benefits**, of the device when used as intended by the manufacturer”

Clinical evidence

- ▶ “means **clinical data** and **clinical evaluation** results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended **clinical benefit(s)**, when used as intended by the manufacturer”

MDR: requirement for clinical evaluation

All classes of medical devices will require a clinical evaluation

- ▶ The requirement for a clinical evaluation can be found in the new Article 61 and in the new Annex XIV, Parts A and B.
- ▶ **Part A is focused on the pre-market phase.** Requirement for:
 - a **Clinical Evaluation Plan** (content is specified);
 - an evaluation of clinical data; and
 - a Clinical Evaluation Report (CER)
- ▶ **Part B is focused on the post market phase:**
 - details the requirements for the **Post Market Clinical Follow-up (PMCF) Plan**; and
 - introduces the requirement for a **PMCF Evaluation Report**.

Clinical Evaluation Plan

- ▶ This should discuss:
 - **general safety and performance requirements (GSPRs)** that require support from relevant clinical data
 - intended purpose of the device;
 - intended target groups
 - methods to be used for examination of clinical safety
 - intended **clinical benefits**
 - parameters to be used to determine, based on the **state of the art** in medicine, the acceptability of the benefit-risk ratio for the various indications
 - benefit-risk issues relating to specific components
 - **clinical development plan** indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations
 - **PMCF** with an indication of milestones

Clinical Evaluation Procedure (MDR Art61)

A "defined and methodologically sound" procedure based on the following:

- a critical evaluation of relevant scientific literature of equivalent devices, if data demonstrate compliance with relevant **GSPRs**
- critical evaluation of results of all available clinical investigations (particularly if conducted according to the relevant **MDR procedures**)
- consideration of currently available **alternative treatment options**

Clinical data SOURCES FOR CLINICAL EVALUATION

- ▶ Information concerning safety or performance should be sourced from:
 - ▶ clinical investigation(s) of the device concerned
 - ▶ clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated
 - ▶ reports published in **peer-reviewed*** scientific literature on other clinical experience of either the device in question or an equivalent device
 - ▶ **clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up (PMCF)***

* new to MDR

Clinical data for implantable and Class III devices

- ▶ Should be sourced from **sponsor-led clinical investigations**

Exceptions:

- the device is modified, but equivalent to a device already marketed by the same manufacturer
- ▶ If clinical data relating to an **equivalent** device marketed by **another manufacturer** is to be used, it will be necessary to demonstrate that:
 - the two manufacturers have a **contract** in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis;
 - the original clinical evaluation was performed in compliance with MDR.

MDR - Clinical Investigations

Chapter VI Art 61- 82

Art 61	Clinical Evaluation
Art 62	General requirements regarding clinical investigation
Art 63 - 66	Ethics: Informed consent, vulnerable groups
Art 68	Clinical investigations in emergency situations
Art 69	Damage compensation
Art 70	Applications for clinical investigation
Art 72	Conduct of clinical investigation
Art 75	Substantial modifications to clinical investigations
Art 76	Corrective measures by Member States
Art 77	Information from Sponsor at end of clinical investigation
Art 78 - 79	Assessment procedures
Art 80	Recording and reporting adverse events

MDR – clinical investigation annex

- ▶ **Annex XIV – Clinical Evaluation & PMCF**
 - ▶ Part B – Post Market Clinical Follow-up
- ▶ **Annex XV – Clinical Investigation**
 - ▶ Chp 1 – General requirements
 - ▶ Ethics
 - ▶ Methods
 - ▶ Chp 2 – Documentation regarding the application for CI
 - ▶ Application Form
 - ▶ Investigator Brochure
 - ▶ Clinical Investigation Plan
 - ▶ Chp 3 – Other obligations of Sponsor
 - ▶ Retention documentation
 - ▶ Monitoring
 - ▶ Follow-up subjects
 - ▶ GCP compliance with internal/external inspection
 - ▶ Clinical Investigation Report

MDR - CLINICAL INVESTIGATION SUMMARY

Required Clinical Evaluation Plan & Clinical Development Plan (Annex XIV Pt A)

- ▶ Specific requirements for vulnerable or incapacitated subjects
- ▶ Clear rationale for sample size
- ▶ Timelines for reporting Serious Adverse Events
- ▶ Personal Data Privacy, GDPR
- ▶ Centralised system for registration of clinical studies

NOTE: *SOME* devices will be up-classified requiring investigations

Examples of new class III designations under MDR include:

- active implantable devices or their accessories
- surgical meshes
- software which is used to take decisions that may directly or indirectly cause death or irreversible deterioration of health
- devices incorporating or consisting of nanomaterial if they present a high or medium potential for internal exposure

MDR: Exempt implantable and class III devices; other devices

- ▶ The requirement to perform clinical investigations will not apply to the following:
 - Sutures, staples, dental fillings/braces/crowns, screws, wedges, plates, wires, pins, clips or connectors - for which the clinical evaluation is based on sufficient clinical data and is in compliance with the relevant product-specific common specification

Non-implantable and non-class III devices

- ▶ Manufacturers of who wish to use clinical data relating to **equivalent** devices will not require a contract but will need to demonstrate "sufficient levels of access".

MDR: Legacy products

- ▶ The requirement to perform clinical investigations will not apply to implantable and class III devices which have been lawfully placed on the market or put into service in accordance with MDD or AIMDD and for which the clinical evaluation:
 - ▶ is based on **sufficient clinical data**
 - ▶ is in compliance with the relevant product-specific common specification for the clinical evaluation of that kind of device, where such a common specification is available
- ▶ In some cases, data accepted under the current MDD may no longer be acceptable under the new MDR:
 - ▶ PMCF studies could help bridge the gap in clinical data.

PMCF should be proactive

- ▶ Most of MEDDEV 2.12/2 has been incorporated into the MDR, but where MEDDEV 2.12/2 talks about a “PMCF study”, the MDR refers to “PMCF investigations” to clarify that there is little difference between a clinical investigation and a PMCF investigation.
- ▶ The protection of subjects and high ethical standards required for a clinical investigation should also be applied in a PMCF investigation.
- ▶ When conducting PMCF, the manufacturer “shall **proactively** collect and evaluate clinical data (...) with the aim of:
 - confirming the safety and performance throughout the expected lifetime of the device;
 - ensuring the continued acceptability of identified risks; and
 - detecting emerging risks”
- ▶ PMCF data will be used to update the clinical evaluation report throughout the life cycle of the device.

Key changes in Clinical Evaluation requirements

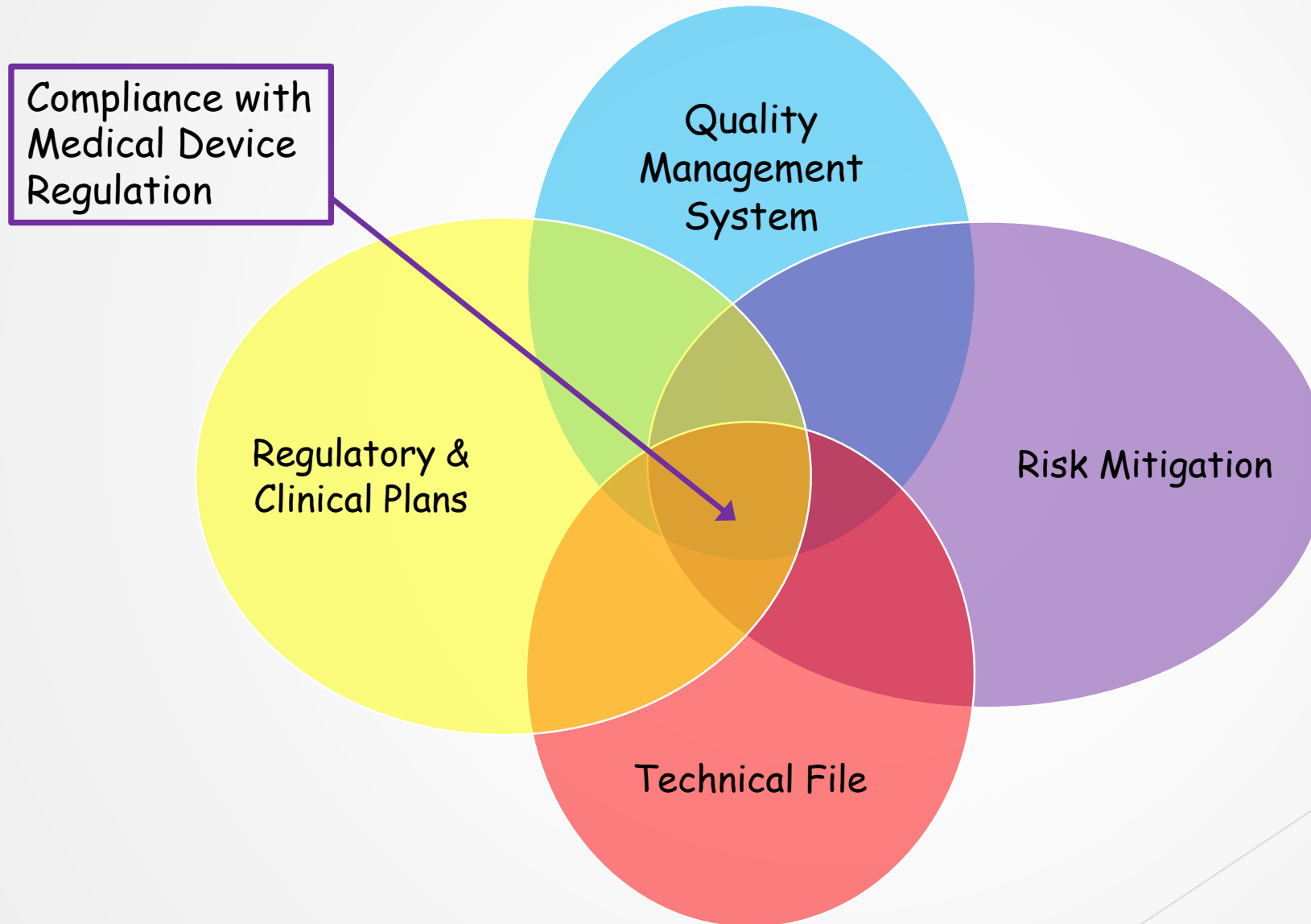
- Strong emphasis on the **Clinical Evaluation Plan**
- Clinical data must be compliant with **GSPRs**
- Data from clinical investigations performed according to **MDR procedures**
- Results should be analysed in the context of **current medical practice/SOA**
- Data from PMS, in particular **PMCF** should be included
- Clinical evaluation should verify device safety and performance, including **clinical benefits**

Key changes affecting the need for clinical investigations

The MDR is enforcing and extending the requirement for clinical studies by:

- extending the range of devices that will require clinical investigations (due to **up-classification**)
- effectively **blocking the equivalence** route for most implantable and class III devices.
- making it clear **clinical benefits**, in addition to safety and performance have to be demonstrated
- emphasising the need for proactive **PMCF investigations**

Device Process Overview



Preparing for the MDR

- All manufacturers should be executing their transition plan to MDR now as organisational delays may lead to a delay in CE marking or withdrawal of CE mark
- A manufacturer who is fulfilling current MEDDEV guidelines will be well prepared for MDR **clinical evidence** compliance
- All manufacturers should ensure internal personnel or external consultants have been identified who meet clinical evaluator requirements under MEDDEV 2.7/1 Rev 4
- Clinical evaluations should be performed according to MEDDEV 2.7/1 Rev 4 if possible
 - However, be aware that Notified Bodies vary in the importance they place on MEDDEV 2.7/1 Rev. 4-compliance
- Small and medium-sized companies should be aware that new rules, especially the increased requirement for clinical investigations may have an impact on margins and lead to higher product costs

Thank You

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