

The Role of Notified Bodies in Clinical Investigations under the MDR/IVDR and ISO 14155/ISO 20916

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Mehr Wert.
Mehr Vertrauen.

Innsbruck 30-09-2026

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At a glance

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The Role of Notified Bodies in Clinical Investigations under the MDR/IVDR and ISO 14155/ISO 20916

01 Role of the Notified Body/ Tasks and Assessment Areas of the Notified Body

02 MDR vs. IVDR – Regulatory Framework

03 Clinical Investigations under the MDR/ ISO 14155 – Good Clinical Practice for Medical Devices

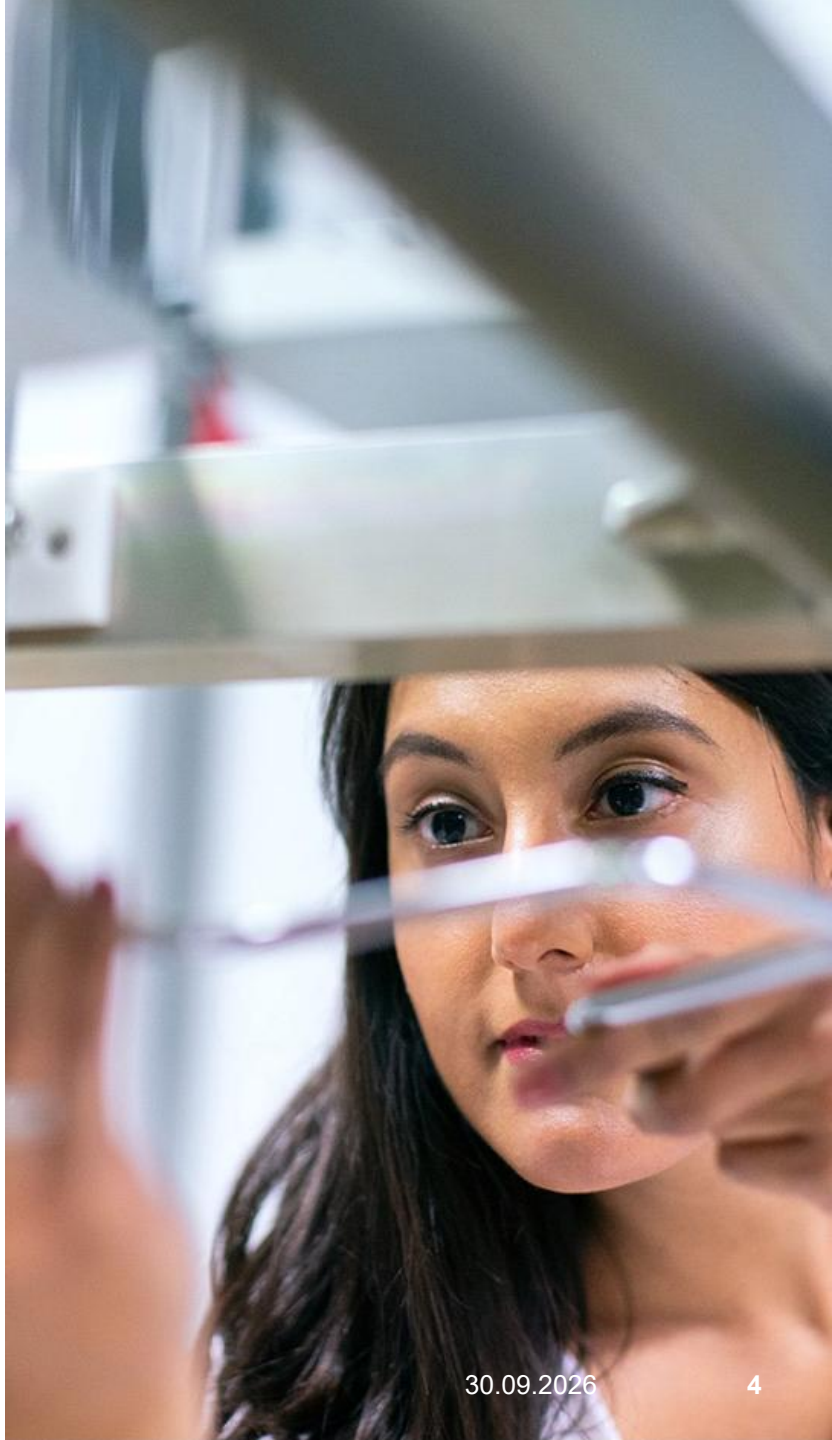
04 Performance Studies under the IVDR/ Performance Studies under the IVDR

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1. Role of the Notified Body/ Tasks and Assessment Areas of the Notified Body

- Purpose and responsibilities of the Notified Body
- Role in conformity assessment and regulatory oversight
- Interaction with manufacturers and clinical investigation sponsors
- Assessment of clinical and performance evaluation documentation
- Review of clinical investigation and performance study documentation
- Assessment of risk management and benefit-risk determination
- Review of data integrity and traceability
- Assessment of compliance with applicable regulatory and quality requirements



1. Role of the Notified Body

Purpose and Responsibilities of the Notified Body

- Conduct MDR-compliant conformity assessments
- Assess manufacturer and device compliance with regulatory requirements
- Review the QMS and technical documentation
- Evaluate clinical evidence and clinical evaluation

MDR Annex VII – „Requirements to be met by Notified Bodies

Role in conformity assessment and regulatory oversight

- Certification & Accreditation: Review evidence and issue or maintain certificates.
- Regulatory Surveillance: Monitor ongoing compliance.
- Inspections & Audits: Conduct assessments to identify non-compliance

IVDR (EU) 2017/746 ist Annex VII – „Requirements to be met by Notified Bodies“.

Interaction with Manufacturers and Clinical Investigation Sponsors

- Communicates regulatory and conformity assessment requirements
- Reviews documentation and assessment findings
- Coordinates with manufacturers and sponsors on audits and corrective actions
- Maintains independence and impartiality throughout the assessment process

1. Role of the Notified Body

Annex VII

4.5.1. General

The notified body shall have **expertise**, facilities and documented procedures that **are sufficient to effectively conduct the conformity assessment activities** for which the notified body in question is designated, taking account of the relevant requirements set out in Annexes IX to XI, and in particular all of the following requirements:
– **plan and periodically carry** out **appropriate surveillance audits** and assessments, carry out or request certain tests to verify the **proper functioning of the quality management system** and to perform unannounced on-site audits

- **Expertise:**
  Clinical aspects require specific sufficient expertise = see qualification requirements of clinical auditors.

- **Appropriate surveillance audits:**
  = this has to consider that for class III, implantable and rule 12 devices more requirements of MDR, MDCG need to be considered as for other devices.
  Additional surveillance activities fulfil this requirement = clinical audits.

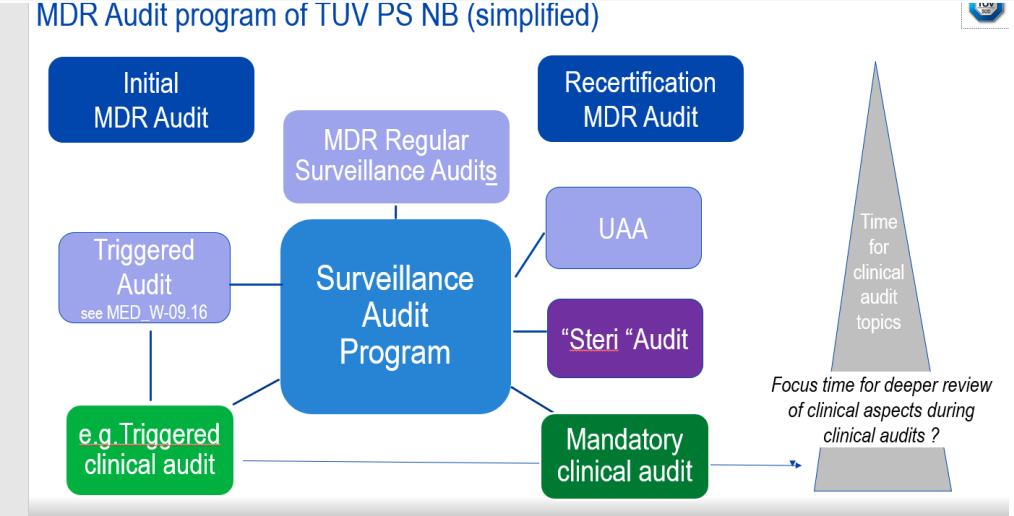
4.5.2. Quality management system auditing
(b) Based on the **audit program** it has drawn up, **the notified body shall**, in accordance with its documented procedures:
– **audit the manufacturer's quality management system**, in order to verify that the quality management system ensures that the devices covered conform to **the relevant provisions of this Regulation which apply to devices at every stage, from design through final quality control to ongoing surveillance**, and shall determine whether the requirements of this Regulation are met.

It is the obligation of the NB to draw up an **appropriate audit program.**
The relevant provisions of MDR towards the manufacturers QMS and our approach of an ongoing surveillance program are different from device to device
= clinical audits for some Manufacturer QMS ensure that extended requirements of MDR, MDCG (particularly for high risk devices) are addressed appropriately by experienced clinical auditors and adequate clinical audit scope

1. Role of the Notified Body

Duties of NB - Conformity Assessment Program drawn up by NB

Annex IX	Our designated approach
3.3 Notified bodies shall periodically, **at least once every 12 months**, carry out **appropriate audits** and assessments to make sure that the manufacturer in question applies the approved quality management system and the post- market surveillance plan.	MDR does not speak about one surveillance audit per year. Moreover, MDR expects at least one audit every 12 months, and expects appropriate audits = clinical audits are an integral part of the surveillance program that includes as well the specific requirements on PMS including PMCF. Mandatory clinical audits are carried out once in three years. Triggered audits are additional elements of the surveillance program



1. Role of the Notified Body

Additional Procedures – To Be Performed by Notified Bodies MDR Articles 52 and 54 in conjunction with Annexes IX and X

Class III implants and Class IIb (Rule 12)

- Consultation procedure in connection with the clinical evaluation (Article 54) involving the Commission's expert panel.

Medicinal substance component

- Consultation procedure with the competent authority or the European Medicines Agency (EMA)
- If derived from human blood or plasma → involvement of the Notified Body also in batch release

Tissues or cells of animal or human origin, or their derivatives

- Consultation procedure with the competent authority or the European Medicines Agency (EMA)

Products or their metabolites that are systemically absorbed by the human body to achieve their intended purpose

- Consultation procedure with the competent authority or the European Medicines Agency (EMA)

1. Role of the Notified Body

Additional Procedures – To Be Performed by Notified Bodies

IVDR Article 48 in conjunction with Annexes IX and X

Class D devices

- Consultation with the competent authority or the European Medicines Agency (EMA) for companion diagnostics (CDx).
- Laboratory verification by an EU Reference Laboratory (EURL) for devices for which an EU Reference Laboratory has been designated.
- Consultation of relevant expert panels where no Common Specifications (CS) are available and it is the first certification of that type of Class D device

Verification of the manufacturer's claimed performance and compliance with applicable Common Specifications (CS) by an EU Reference Laboratory.
Testing focuses in particular on analytical and diagnostic sensitivity, using the best available reference materials

Class D devices – EU Reference Laboratory

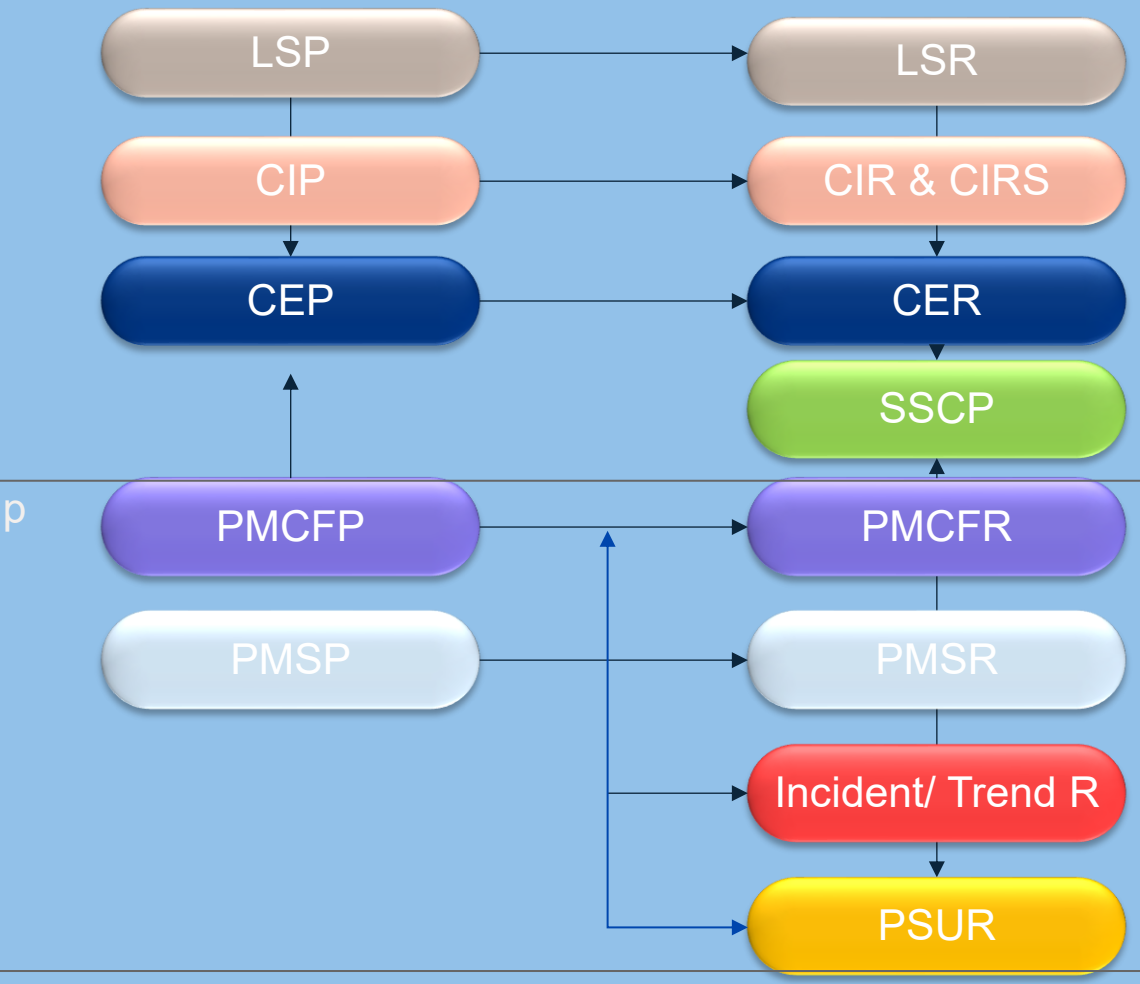
Companion Diagnostics (CDx)

- Consultation with the competent authority designated under Directive 2001/83/EC or with the EMA, as applicable.
- The consultation concerns the conformity assessment of the CDx and the associated medicinal product

If no CS are available and it is the first certification for that type of device, the Notified Body consults the relevant experts regarding the manufacturer's performance evaluation report

Class D devices without Common Specifications

Clinical Aspects: Process, Plans, Reports, Summaries



References in MDR
As well Art. 7, 8 , 9, 10, 15, 18

Annex VII, XIV.1

Art. 61, 62-80, 82
Annex XV

Art. 61
Annex II, XIV, IX

Art. 32 and 61.11

Art. 61.11,
Annex III, XIV, IX

Art. 61.11, 84, 85,
Annex III, XIV, IX

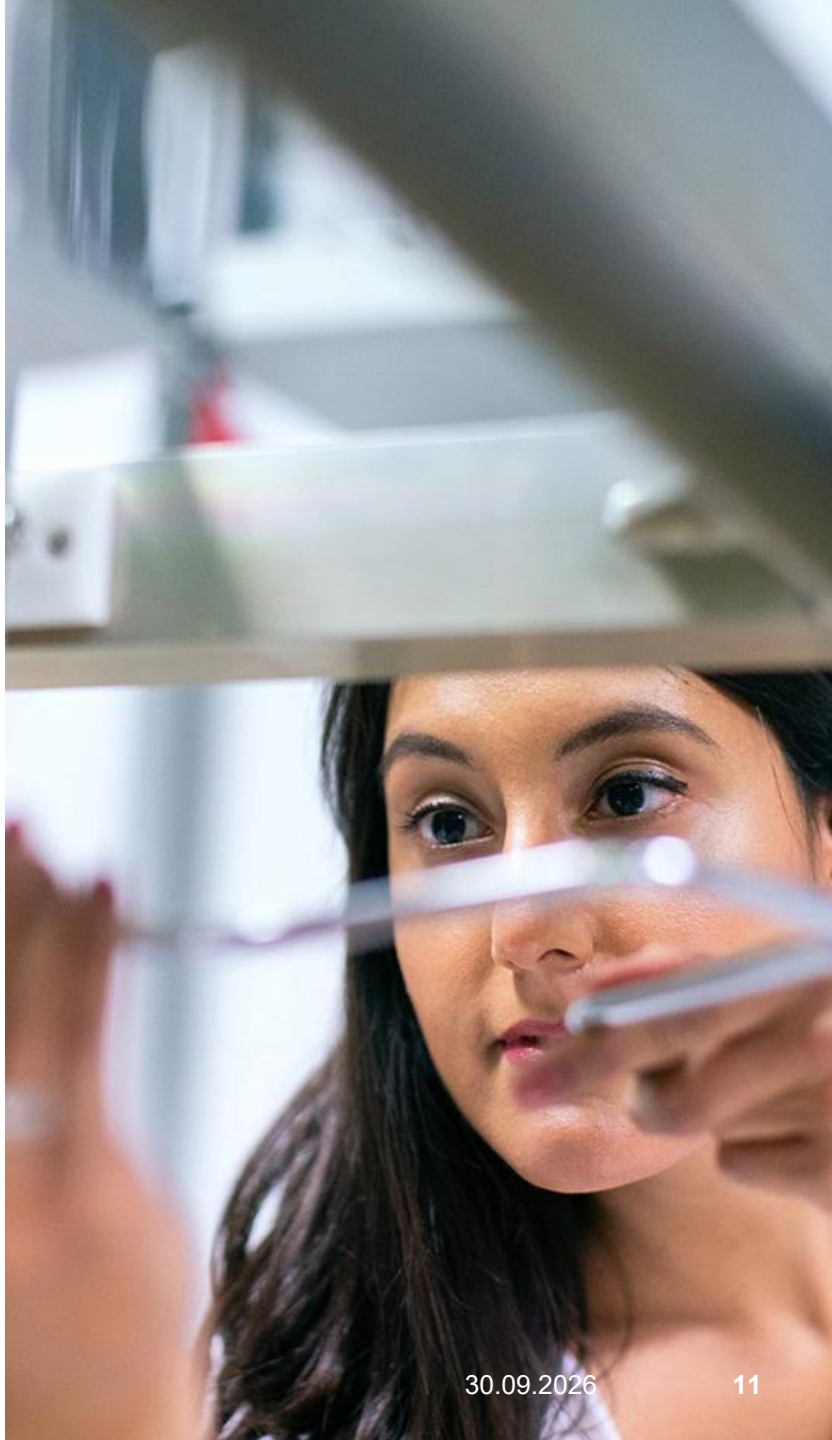
Art. 87, 88, 89, 92
Annex IX, III

Art. 86, 92
Annex IX, III

Consider Art. 120.3

2. MDR vs. IVDR – Regulatory Framework

- Overview of the EU Medical Device Regulation (MDR)
- Overview of the EU In Vitro Diagnostic Medical Devices Regulation (IVDR)
- Key regulatory principles and differences



2. MDR vs. IVDR – Regulatory Framework



What is the MDR?

- Mandatory requirement for selling medical devices in the EU.
- Harmonizes the review and approval process in member states.

Key requirements

- Medical devices approved under old directives are not exempt.
- Legacy devices still being sold must be recertified under the MDR.
- Except for Class I devices, manufacturers must involve an EU Notified Body such as TÜV SÜD.

Timeline

- MDR became applicable to all medical devices sold in the EU in May 2021.

Considerations

- Anticipate delays due to the expanded scope of medical devices that require notified body involvement.
- Consult with a notified body, such as TÜV SÜD, early on during product development.

2. MDR vs. IVDR – Regulatory Framework



What is the IVDR?

EU regulatory legislation for:

- Placing in-vitro diagnostic devices on the market.
- Making them available.
- Putting them into service.

Key requirements

- Effective now in all EU and EFTA states.
- No need to be transposed into the law of respective states

Obligation	IVDR QMS in place acc. IVDR Art. 10(8).	Lodge an application for IDVR conformity assessment.	Sign a written agreement & transfer appr. surveillance to IVR NB.	End of transition period.	Sell-off
IVDD certified or Class D	26th May 2025	26th May 2025	26th September 2025	31st December 2027	No limitation in time other than device expiry date/stock availability.
Class C	26th May 2025	26th May 2026	26th September 2026	31st December 2028	No limitation in time other than device expiry date/stock availability.
Class B & A sterile	26th May 2025	26th May 2027	26th September 2027	31st December 2029	No limitation in time other than device expiry date/stock availability.

TransitionTimeline

- Applies to specific “legacy” devices.
- Transition period depends on device classification and if previous CE-marking was by self-declaration or notified body certification

Considerations

- Ensure your quality management system complies.
- Prepare your technical documentation.
- Engage with us early on to discuss your needs

2. MDR vs. IVDR – Regulatory Framework

175 Pages
101 Wheras
71 Definitions
10 Chapter
123 Articles
17 Annexes

MDR 2017/45

→ **Update of MS Law**

Delegating Acts

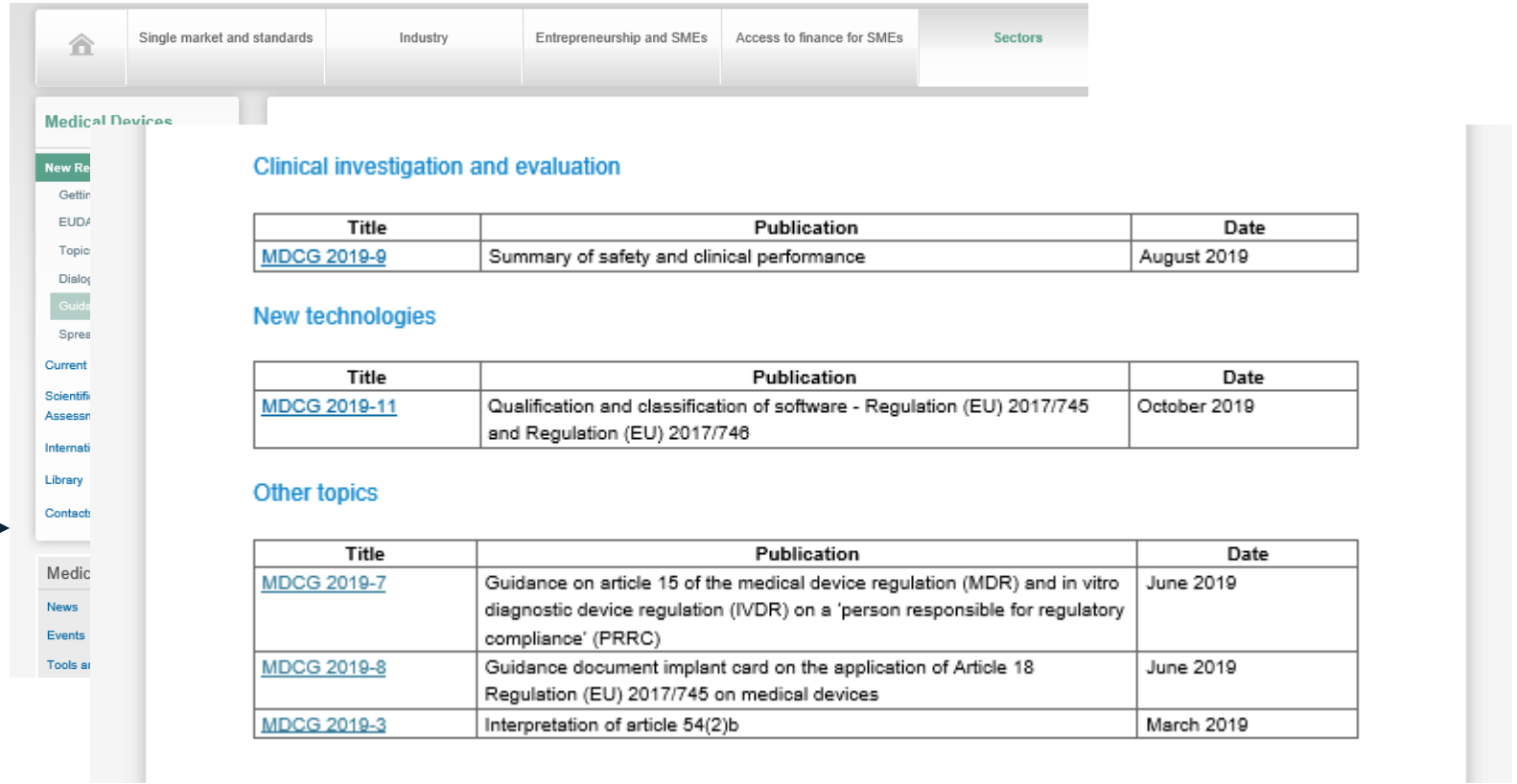
Implementing Acts

Harmonized Standards, Art. 8

Common Specification, Art. 9

Other guidance documents e.g. MDCG (Status approx. 30 published)

https://ec.europa.eu/growth/sectors/medical-devices/new-regulations/guidance_en



Clinical investigation and evaluation

Title	Publication	Date
MDCG 2019-9	Summary of safety and clinical performance	August 2019

New technologies

Title	Publication	Date
MDCG 2019-11	Qualification and classification of software - Regulation (EU) 2017/745 and Regulation (EU) 2017/746	October 2019

Other topics

Title	Publication	Date
MDCG 2019-7	Guidance on article 15 of the medical device regulation (MDR) and in vitro diagnostic device regulation (IVDR) on a 'person responsible for regulatory compliance' (PRRC)	June 2019
MDCG 2019-8	Guidance document implant card on the application of Article 18 Regulation (EU) 2017/745 on medical devices	June 2019
MDCG 2019-3	Interpretation of article 54(2)b	March 2019

2. MDR vs. IVDR – Regulatory Framework

Delegating Acts (12)

Implementing Acts (11)

MDR: Implementing Acts – several implementing acts adopted by the European Commission to support the practical implementation of the MDR

Common Specifications 2

Harmonised Standards Ca.40

MDCG Guidance

2. MDR vs. IVDR – Regulatory Framework

IVDR

Delegating Acts
(0)

Implementing Acts
(7)

Common Specifications
1

Harmonised Standards
Ca.23

EU Reference Laboratories (EURLs)
3 relevant acts – 2022/944, 2022/945 and 2023/2713

2. MDR vs. IVDR – Regulatory Framework

Delegating Acts & Common Specifications

1	Delegated	Art. 1(5)	Products without a medical purpose – Annex XVI	Delegated power
2	Delegated	Art. 3	Definition of certain terms, e.g. nanomaterials	Delegated power
3	Delegated	Art. 10(4)	Manufacturer obligations / quality-management-related requirements	Delegated power
4	Delegated	Art. 18(3)	Implant card – exemptions / information requirements	Delegated power
5	Delegated	Art. 19(4)	EU Declaration of Conformity	Delegated power
6	Delegated	Art. 27(10)	UDI system / UDI requirements	Delegated power
7	Delegated	Art. 44(11)	Conformity-assessment procedures	Delegated power
8	Delegated	Art. 52(5)	Specific conformity assessment for certain Class IIb/III devices	Delegated power
9	Delegated	Art. 56(6)	Certificates of conformity	Delegated power
10	Delegated	Art. 61(8)	Clinical evaluation	Delegated power
11	Delegated	Art. 70(8)	Clinical-investigation application procedure	Delegated power
12	Delegated	Art. 106(15)	Expert panels / scientific advice	

Commission Implementing Regulation (EU) 2020/1207 – Common Specifications for the reprocessing of single-use devices.

Commission Implementing Regulation (EU) 2022/2346, as amended by Commission Implementing Regulation (EU) 2023/1194 – Common Specifications for products without an intended medical purpose listed in Annex XVI of the MDR

Delegated vs. implemented

Delegated Acts modify or supplement the legal framework within a specific delegated power, whereas Implementing Acts establish detailed and uniform rules for putting the existing framework into practice

2. MDR vs. IVDR – Regulatory Framework

Implementing Acts & Implementing Acts vs. MDGC Guidance

MDCG not legally binding for manufacaturers

Implementing Acts are legally binding EU legislation, whereas MDCG Guidance provides non-binding regulatory interpretation and practical guidance.

Nevertheless, MDCG Guidance is highly relevant in practice, as it reflects the common regulatory understanding of the MDCG and can strongly influence the expectations of Competent Authorities and Notified Bodies

MDCG binding for NB

Art. 9	Implementing	Common Specifications (CS)	EU 2020/1207; EU 2022/2346	
Art. 17(5)	Implementing	Reprocessing of single-use devices	EU 2020/1207	
Art. 42(13)	Implementing	Codes / scope of designation of Notified Bodies		EU 2017/2185
Art. 52(14)	Implementing	Detailed arrangements for conformity assessment by NBs		Implementing power
Art. 61(13)	Implementing	Uniform application of clinical evaluation	Implementing power	
Art. 70(8)	Implementing	Clinical-investigation procedures / coordinated assessment		Implementing power
Art. 81	Implementing	Detailed arrangements for clinical investigations		Implementing power
Art. 91	Implementing	Vigilance / PMS arrangements	Implementing power	
Art. 96	Implementing	Evaluation of national measures	Implementing power	
Art. 97	Implementing	Measures concerning non-compliance	Implementing power	
Art. 98	Implementing	Preventive health-protection measures	Implementing power	
Art. 100	Implementing	Electronic system / market surveillance	Implementing power	

Implementing Act:
The European Commission Implementing Regulation for **EUDAMED**. Such an act forms part of EU law and is legally binding and must therefore be applied accordingly.

MDCG Guidance:
MDCG published guidance on tEUDAMED topic. These documents are intended to help manufacturers, Notified Bodies, and Competent Authorities interpret and apply the MDR consistently in practice. However, they **do not constitute additional EU legislation** and are generally not legally binding.

2. MDR vs. IVDR – Regulatory Framework

MDCG Guidance

- MDCG 2019-7 PRRC – Art. 15
- MDCG 2024-3 Clinical Investigation Plan Synopsis Template &Guidance on content of the Clinical Investigation Plan for clinical investigations of medical devices
- MDCG 2024-5 Guidance on the Investigator's Brochure content
- MDCG 2019-9 Summary of Safety and Clinical Performance
- MDCG 2020-7 PMCF-Plan
- MDCG 2020-6 Sufficient Clinical Evicence for Legacy Device
- MDCG 2020-7 PMCF-Plan
- MDCG 2020-6 Sufficient Clinical Evidence for legacy devices
- MDCG 2020-8 PMCF-Report
- MDCG 2021-28 Substantial modification of clinical investigation under Medical Device Regulation
- MDCG 2019-9 Summary of Safety and Clinical Performance
- MDCG 2020-10/1&2 Safety Repor in Frame of Clinical Investigations
- MDCG 2020-10/1&2 Safety Reporting in Frame of Clinical Investigations
- MDCG 2020-10/1&2 Safety Reporting in Frame of Clinical Investigations
- MDCG 2020-6 Sufficient Clinical Evidence for legacy devices
- MDCG 2021-20-5 Instructions for generating CIV-ID for MDR Clinical Investigations
- MDCG 2021-3 Custom Made Devices
- MDCG 2021-6 Rev. 3 Q&A regardiing Clinical Investigation
- 2023/C 163/06 Commission Guidance on the content and structure of the summary of the clinical investigation report
- MDCG 2021-6 Rev. 3 Q&A regardiing Clinical Investigation

2. MDR vs. IVDR – Regulatory Framework

Implementing Acts IVDR

Year	Implementing Act	Main subject
2017	(EU) 2017/2185	Codes and corresponding types of devices for the designation scope of Notified Bodies
2021	(EU) 2021/2078	EUDAMED – detailed arrangements for the European Database on Medical Devices
2022	(EU) 2022/944	EU Reference Laboratories (EURLs) – tasks and criteria
2022	(EU) 2022/945	EURLs – fees
2022	(EU) 2022/1107	Common Specifications for certain Class D IVDs
2023	(EU) 2023/2713	Designation of EU Reference Laboratories
2026	(EU) 2026/977	Uniform requirements for conformity assessment and Notified Bodies (Annex VII)

2. MDR vs. IVDR – Regulatory Framework

EU Reference Laboratories (EURLs)

Commission Implementing Regulation (EU) 2022/944
Tasks and criteria for EU Reference Laboratories

Commission Implementing Regulation (EU) 2022/945
Fees that may be levied by EU Reference Laboratories

Commission Implementing Regulation (EU) 2023/2713
Designation of EU Reference Laboratories

***Main relevance*:**
Class D in vitro diagnostic medical devices

Key EURL activities:

- **Performance verification of certain Class D IVDs**
- **Verification of compliance with applicable Common Specifications**
- **Batch testing**
- **Provision of scientific and technical support to the European Commission and Member States**

EURL categories initially designated:

- **Hepatitis and retrovirus infections**
- **Herpesvirus infections**
- **Bacterial agents**
- **Respiratory virus infections**

2. MDR vs. IVDR – Regulatory Framework

MDCG IVDR relevant

MDCG 2020-16 rev.5	Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746
MDCG 2021-4 rev.1	Application of transitional provisions for certification of class D in vitro diagnostic medical devices according to Regulation (EU) 2017/746
MDCG 2021-22 rev.1	Clarification on "first certification for that type of device" and corresponding procedures to be followed by notified bodies, in context of the consultation of the expert panel referred to in Article 48(6) of Regulation (EU) 2017/746
MDCG 2022-2	Guidance on general principles of clinical evidence for In Vitro Diagnostic medical devices (IVDs)
MDCG 2022-3 rev.1	Verification of manufactured class D IVDs by notified bodies
MDCG 2022-6	Guidance on significant changes regarding the transitional provision under Article 110(3) of the IVDR
MDCG 2022-8	Regulation (EU) 2017/746 – application of IVDR requirements to 'legacy devices' and to devices placed on the ma prior to 26 May 2022 in accordance with Directive 98/79/EC
MDCG 2022-9 rev.1	Summary of safety and performance template
MDCG 2022-10	Q&A on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (C and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)
MDCG 2022-15	Guidance on appropriate surveillance regarding the transitional provisions under Article 110 of the IVDR with regard to devices covered by certificates according to the IVDD
MDCG 2022-19	Performance study application/notification documents under Regulation (EU) 2017/746
MDCG 2022-20	Substantial modification of performance study under Regulation (EU) 2017/746
MDCG 2024-4	Safety reporting in performance studies of in vitro diagnostic medical devices under Regulation (EU) 2017/746
MDCG 2024-11	Guidance on qualification of in vitro diagnostic medical devices
MDCG 2025-5	Questions & Answers regarding performance studies of in vitro diagnostic medical devices under Regulation (EU) 2017/746

Some MDCG documents are MDR/IVDR common

MDCG 2019-7 rev.1 – *Guidance on Article 15 PRRC*

MDCG 2022-16 – *Guidance on Authorised Representatives*

2. MDR vs. IVDR – Regulatory Framework

MDR Chapter VI, Annex XV - Clinical Evaluation/Clinical Investigation

§§ 61 – 82 21 Articles and Annexes

- Art. 61 Clinical Evaluation, Annex XIV Part A
- Art. 62 General requirements regarding clinical investigation
- Art. 63 Informed Consent
- Art. 64 Clinical investigations on incapacitated subjects
- Art. 65 Clinical investigations on minors
- Art. 66 Clinical investigations on pregnant or breastfeeding women
- Art. 67 Additional national measures
- Art. 68 Clinical investigations in emergency situations
- Art. 69 Damage compensation
- Art. 70 Application for clinical investigations
- Art. 71 Assessment by Member States
- Art. 72 Conduct of a clinical investigation
- Art. 73 Electronic system on clinical investigation
- Art. 74 Clinical investigations with devices authorizes to bear the CE marking
- Art. 75 Substantial modification to a clinical investigation
- Art. 76 Corrective measures to be taken by Member States and information exchange between Member States
- Art. 77 Information by the Sponsor at the end of a clinical investigations or in the event of temporary hold or early termination
- Art. 78 Clinical investigations conducted in more than one Member State
- Art. 79 Review of coordinated procedure
- Art. 80 Recording and reporting of adverse events occurring during clinical investigations events
- Art. 81 Implementation act (e.g. forms, categories of devices, timelines)
- Art. 82 Requirements regarding other clinical investigations

Annex VIX Clinical Evaluation and Post market clinical follow up
Annex XV Clinical Investigation

2. MDR vs. IVDR – Regulatory Framework

IVDR Chapter VI, Annex XIII & Annex XIV – Clinical Evidence / Performance Evaluation / Performance Studies

Article 56-77

Chapter VI – Clinical Evidence, Performance Evaluation and Performance Studies

- **Article 56** – Performance evaluation and clinical evidence
- **Article 57** – General requirements regarding performance studies
- **Article 58** – Additional requirements for certain performance studies
- **Article 59** – Informed consent
- **Articles 60–62** – Requirements for specific subject groups and performance-study situations
- **Articles 63–77** – Further requirements for performance-study applications, conduct, reporting, modifications,

Annex XIII – Performance Evaluation, Performance Studies and Post-Market Performance Follow-up

- **Part A – Performance Evaluation and Performance Studies**
  - Performance Evaluation Plan
  - Scientific validity
  - Analytical performance
  - Clinical performance
  - Clinical evidence
  - Performance Evaluation Report
- **Part B – Post-Market Performance Follow-up (PMPF)**

MDCG 2019-7 rev.1 – *Guidance on Article 15 PRRC*

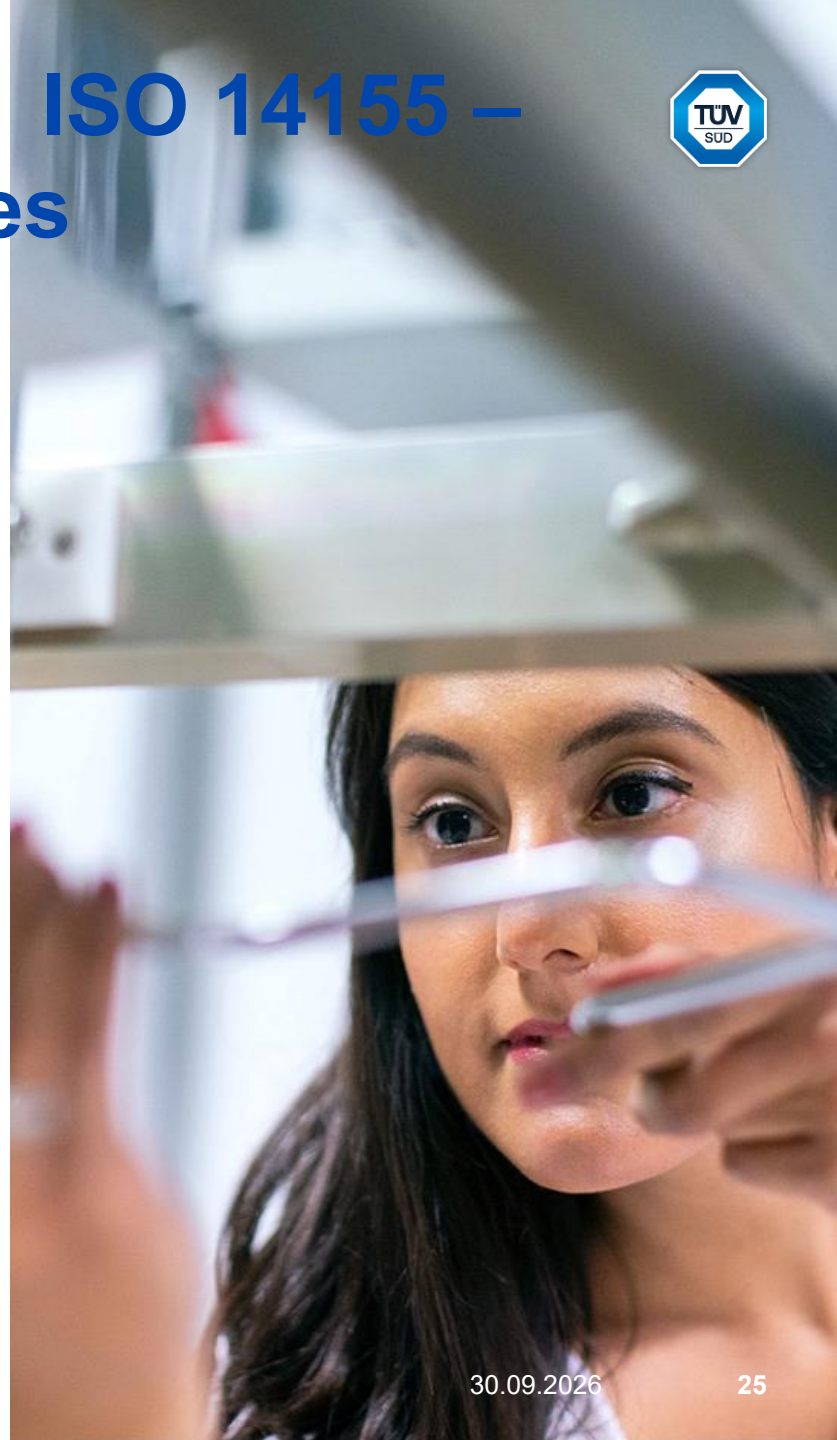
Annex XIV – Interventional Clinical Performance Studies and Certain Other Performance Studies

This covers, among other things:

- **Application documentation**
- **Performance Study Plan**
- **Investigator and sponsor requirements**
- **Informed consent documentation**
- **Requirements for conducting and reporting performance studie**

3. Clinical Investigations under the MDR/ ISO 14155 – Good Clinical Practice for Medical Devices

- Regulatory requirements for clinical investigations (see also chapter 2 Regulatory Framework)
- Clinical Investigation Plan (CIP)
- Sponsor and investigator responsibilities
- Protection of subjects and data integrity
- Purpose and scope of ISO 14155
- Principles of Good Clinical Practice
- Essential requirements for planning, conducting and documenting clinical investigations
- Relationship between ISO 14155 and the MDR



3.Clinical Investigations under the MDR/ ISO 14155

MDR Article 2(45)

(45) 'clinical investigation' means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device;

A "systematic investigation" is typically a predetermined method for studying a specific topic, answering a specific question(s), testing a specific hypothesis(es) or developing theory. Examples of systematic investigations include:

- observational studies
- analysis of existing data or biological specimens
- evaluations of social or educational programs
- group comparison studies
- interventional research

Source: https://www.boisestate.edu/research-compliance/irb/guidance/determining-if-irb-review-is-required/

A systematic investigation involves a methodical procedure and plan, is theoretically grounded, and specifies a focused and well-defined research problem or question, is informed by the empirical findings of others, is analytically robust, and provides a detailed and complete description of data collection methods.

Source: https://cuhs.harvard.edu/definition-research

3.Clinical Investigations under the MDR/ ISO 14155
The value of ISO 14155:2020 - globally

Brazil

National Health Surveillance Agency (ANVISA)

The ISO 14155:2011 is one of the main references to the Resolution RDC 10/2015 published on March 3rd, 2015 for clinic particularly for Goo

The ISO14155:20 the Brazilian guida **in clinical trials a**

Australia

Therapeutic Goods Administration (TGA)

As is common to all ISO14155:2011 is device is free to ch Essential Principles by other means su literature, or using with ISO 14155:201 used to demonst Principles, then a s **If a trial for a devic EP14 is deemed to**

Japan

Ministry of Health, Labour and Welfare (MHLW) Pharmaceuticals and Medical Devices Agency (PMDA)

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In this context, the device GCP issued in February 2013 (No. 0208-1) clearly states that **ISO 14155:2011 is an equivalent standard to the Japanese GCP.** It is noted that GCP inspections (desk-top or on-site inspection) are applied even if the clinical trials are conducted in accordance with ISO 14155: 2011 or other equivalent standards.

HC publishes a list of recognised standards to facilitate the regulatory review of medical device license applications. **Included on the list is the standard entitled "Clinical subjects – 1:2011).** In s are not part of the equirements tice, during **from the applicants ducted** in a



China

China Food and Drug Administration (CFDA)

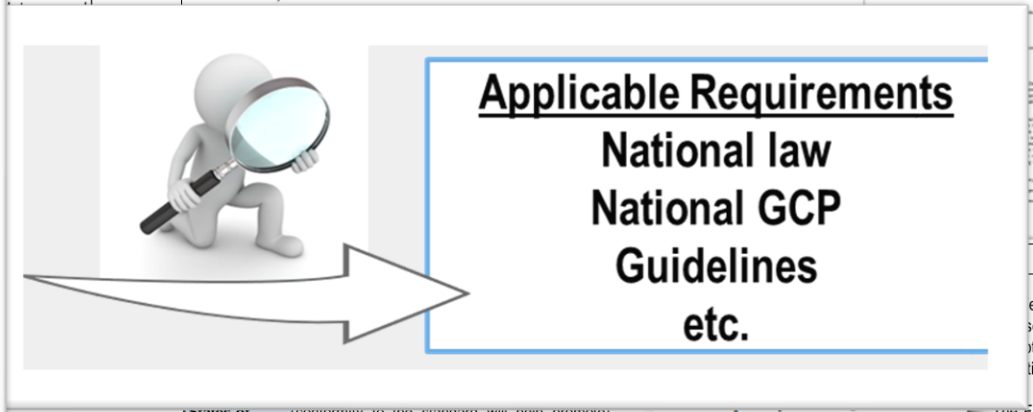
ice industry standard: YY/T 0297-1997, which was equivalent to the ISO 14155:1996, and it is a **recommended standard,** not a mandatory standard. In China, the clinical trials of medical device should comply with the requirements of the provision on medical device clinical trials (SFDA decree No.5) now. CFDA started to draft the medical device GCP(good clinical practice), during the process, we considered the requirements of new version of ISO 14155.

MDR EU 2017_745 whereas (64):

The rules on clinical investigations **should be in line with well-established international guidance in this field, such as the international standard ISO 14155:2011 on good clinical practice for clinical investigations of medical devices for human subjects**, so as to make it easier for the results of clinical investigations conducted in the Union to be accepted as documentation outside the Union and to make it easier for the results of clinical investigations conducted outside the Union in accordance with international guidelines to be accepted within the Union.

In addition, the rules should be in line with the most recent version of the World


REGULATIONS

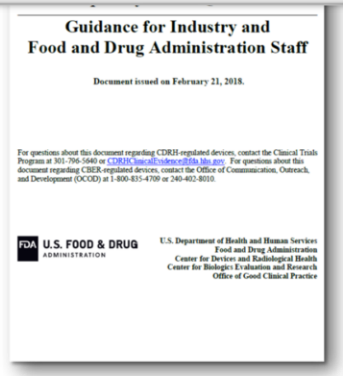


States of America

US Food and Drug Administration (US FDA)

conformity to the standard will help promote harmonization of GCP, and ensure the reliability and integrity of the data submitted in support of marketing applications while ensuring that human research subjects are adequately protected.

In February 2013 FDA published a federal register notice of its proposed rule to amend the current device regulations to require that clinical studies conducted outside the United States in support of marketing applications from FDA be conducted in accordance with GCP. The rule is currently under review however **ISO 14155:2011 has been cited in the notice as a reference to device GCP** which can be used currently and in the future to adequately satisfy potential changes in the regulations.


Guidance for Industry and Food and Drug Administration Staff

Document issued on February 21, 2018.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Center for Biologics Evaluation and Research Office of Good Clinical Practice

ebruary 21, 2018, the FDA ed its final ruling on the otance of data from clinical tigations for medical devices.

The FDA formally opens the path to submit foreign clinical data to secure marketing clearance for medical devices in the U.S

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FDA recognizes the ISO 14155:2011 as a GCP standard for medical device trials conducted outside the U.S

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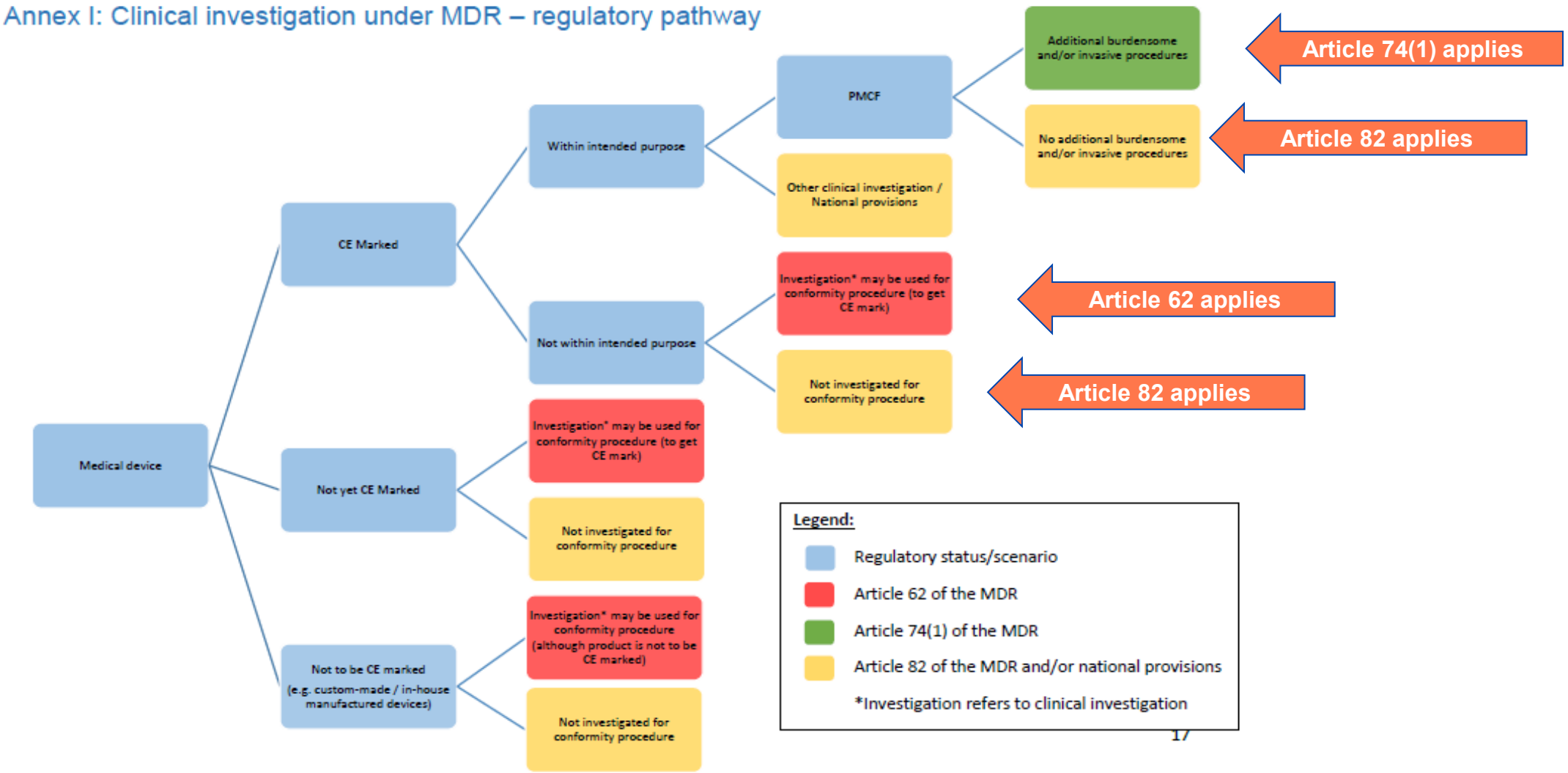
3.Clinical Investigations under the MDR/ ISO 14155

ISO 14155 – Good Clinical Practice for Medical Devices

Region	Regulatory Framework	ISO 14155 Status
European Union	EU MDR 2017/745 (Article 62-82)	Harmonized (EN ISO 14155)
United States	21 CFR Part 812 (IDE)	Recognized; data accepted
Japan	PMD Act	Referenced in clinical investigation guidance
China	NMPA regulations	Accepted for imported device data
Australia	Therapeutic Goods Act	Referenced in TGA guidance
Brazil	ANVISA RDC resolutions	Accepted as GCP standard
Canada	Medical Device Regulations	Recognized by Health Canada

3.Clinical Investigations under the MDR/ ISO 14155

MDCG 2021-6 Clinical Investigation



3.Clinical Investigations under the MDR/ ISO 14155

Art. 74: Clinical Investigations with Devices already CE marked

1) With CE marking, within intended use

- ❑ where the investigation would involve submitting subjects to **procedures additional** to those performed under the normal conditions of use of the device and those additional procedures are **invasive or burdensome**, sponsor has to **notify** the MS **at least 30 days before** commencement

follow Annex XV and Articles: 62 (4 b-k&m); 75 (modification); 76 (MS exchange); 77 (end/hold/early termination of CI); 80 (5) Incidence/vigilance reporting applies)
Corrigendum 2019: and 80(6) causal relationship between SAE and the CI procedure

2) With CE marking but other purpose like intended use (out of scope)

3) With CE marking, within intended use

- ❑ Not mentioned how to proceed if no additional invasive and no burdensome procedure occurs

follow Art. 62-81, Annex XV

MS level country specific requirements to be expected (e.g. ECs involvement, insurances)

ISO 14155: 2020 - Burdensome



Annex I.6.1 General

- Clinical investigations can further be categorized by their nature of interference with normal clinical practice as further defined hereunder.
- These categorisations are usually referred to for defining the requirements of ethical considerations (see further information in I.7).

- See as well MDR Art. 74 and 82

I.6 Burden to subjects

Clinical investigations can further be categorized by their nature of interference with normal clinical practice as further defined hereunder. These categorisations are usually referred to for defining the requirements of ethical considerations (see further information in I.7).

I.6.1 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 clinical investigation plan. Diagnostic or monitoring procedures are applied as described in the clinical investigation plan.

Annex I.6.2 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

ISO 14155: 2020 - Not Burdensome



Annex I.6.3 Non-interventional clinical investigation

Non-interventional clinical investigation is a post-market 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.

NOTE: In general, “observational” clinical investigations are “non-interventional”.

I.6.2 Non-interventional clinical investigation

Non-interventional clinical investigation is a post-market 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 clinical investigation plan 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.

NOTE The term “non-interventional” is synonymous with “observational”.

3.Clinical Investigations under the MDR/ ISO 14155

Annex XV Clinical Investigation

Other information regarding the application for clinical investigation:

A signed statement that the device conforms to GSPR covered by the clinical investigation and every precaution to protect the health and safety of the subject

Copy of the opinion(s) of the ethics committee(s) or asap., according to national law

Proof of insurance according to national law

Documents to obtain informed consent (process described in CIP)

Description of the arrangements to comply with the applicable rules on the protection and confidentiality of personal data

Available technical documentation
(e.g. risk analysis/management documentation or specific test reports, upon request)

3.Clinical Investigations under the MDR/ ISO 14155

Annex XV Clinical Investigation

Other sponsor's obligations:

Keep available for the competent national authorities any documentation necessary to provide evidence for the application

Have an agreement in place to ensure SAE are reported to the sponsor in a timely manner

Retention of documents 10 years after end of the CI or at least 10 years last device has been placed on market (15 years for implants)

Provide evidence to assure that the investigation is being conducted in line with Good Clinical Practice e.g. by internal or external auditing/inspection

Appoint an independent monitor to ensure conduction of the investigation (acc. CIP, GCP)

Complete the follow up of investigation subjects

Prepare a clinical investigation report (CIR) and Summary (SCIR)

3.Clinical Investigations under the MDR/ ISO 14155

Registration of CI in publicly accessible database

- In accordance with the Declaration of Helsinki,
  a description of the clinical investigation shall be registered in a publicly accessible database
- before the start of recruitment activities and
- the content shall be updated throughout the conduct of the clinical investigation and
- the results entered at completion of the clinical investigation.

- NOTE: National regulations can apply concerning the timing of registration or updating of the contents.

- See MDR EUDAMED Art. 73

3.Clinical Investigations under the MDR/ ISO 14155
MEDDEV 2.12/2 – PMCF Studies + Anhang XIV Teil B

PMCF Study Requirements

MDCG –2020 -7 MEDDEV 2.12/2
PMCF studies must be outlined as a well designed clinical investigation plan or study plan, and, as appropriate, include:
clearly stated research question(s),objective(s) and related endpoints;
scientifically sound design with an appropriate rationale and statistical analysis plan;
a plan for conduct according to the appropriate standard(s);
a plan for an analysis of the data and for drawing appropriate conclusion(s).”

+

A PMCF study should INCLUDE at minimum:
Sample size,
Study population
Endpoints,
Inclusion/exclusion criteria

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Well Deigned PMCF Study

3.Clinical Investigations under the MDR/ ISO 14155
MEDDEV 2.12/2 – PMCF Studies +Anhang XIV Teil B

Population	Have all patients been considered, Are patients representative of the use of the device withing intended purpose
	Was the sample size sufficient, was the sample size calculated
Intervention	Hast the device been used in accordance with the manufacturer´s labelling?
Objectives	Are they clearly defined and measurable
Outcome/ endpoints	Are the outcome measures clearly defined and does the data support the clinical benfit, safety and performance endpoints and claims
Interventional or observational	Has the study design been justified, if interventional are there any procedures that impact the outcome (e.g. introduce abias)?
Length of observations	Is the length of study sufficient to support the lifetime of the device
Follow up	Does the study include a follow up and if so is the period clinically relevant
Data analysisi	Are the data analysis methods defined? Have the rigth correct statistical method been applied? Does the study plan state how missing data will be handled?

4. Performance Studies under the IVDR/ ISO 20916 – Good Study Practice for IVDs

Study Category	Statutory Citation	Submission Type	Filing Mechanism	Statutory Review Timeline	Ethics Committee Requirement
Surgically Invasive Sampling Solely for Study	Art. 58(1)(a) & Art. 66	Full Application	CA Portal / EUDAMED (CIV-ID)	10-day validation; immediate start after validation where sampling poses no major clinical risk (Art. 66(7)(a), MDCG 2025-5 Q25), otherwise 45 days (+20-day extension)	Mandatory positive opinion (Art. 58(3))
Interventional Study (Results Guide Care)	Art. 58(1)(b) & Art. 66	Full Application	CA Portal / EUDAMED (CIV-ID)	10-day validation + 45 days (+20 day extension)	Mandatory positive opinion (Art. 58(3))
Study Involving Additional Subject Risks	Art. 58(1)(c) & Art. 66	Full Application	CA Portal / EUDAMED (CIV-ID)	10-day validation + 45 days (+20 day extension)	Mandatory positive opinion (Art. 58(3))
Companion Diagnostic (Prospective / Non-Leftover)	Art. 58(2) & Art. 66	Full Application	CA Portal / EUDAMED (CIV-ID)	10-day validation + 45 days (+20 day extension)	Mandatory positive opinion (Art. 58(3))
Companion Diagnostic (Leftover Samples Only)	Art. 58(2)	Prior Notification	CA National Portal	Immediate / Member State acknowledgment	Governed by national law (MDCG 2025-5 Q17)
PMPF on CE-Marked IVD with Invasive/Burdensome Procedures	Art. 70(1)	Prior Notification	CA National Portal	At least 30 calendar days before study start	Governed by national law / Ethics review
PMPF on CE-Marked IVD without Added Burden	Art. 56 & Annex XIII	None (QMS Record)	Internal QMS / PMPF Plan	No prior CA filing required	Governed by national law / Local ethics
Specimen-Only Analytical Study (Leftover Samples)	Art. 57	None	Internal Study File (ISO 20916)	No prior CA filing required	National biobank & consent law (MDCG 2025-5 Q15)

4. Performance Studies under the IVDR/ ISO 20916 – Good Study Practice for IVDs

What Makes a Study Interventional

test results are blinded, batched, or generated post-hoc without disclosure to the treating physician

Prospective Collection NOT Interventional

No study driven intervention

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no interventional clinical performance study

Direct Therapeutic Guidance:

- **Test results determine the patient's treatment: subject receives a drug, surgical procedure, radiation therapy, or immunotherapy**

Withholding or Altering Established Therapy:

- **Test result delay, replace or withhold standard care.**

blood draw or biopsy performed *solely* for the study

Escalation or De-escalation Protocols

- **Test results change monitoring or treatment doses; chemotherapy dosages, or immunosuppressive drug titration**

full application under Article 58(1)(a)

Randomized Diagnostic Strategies:

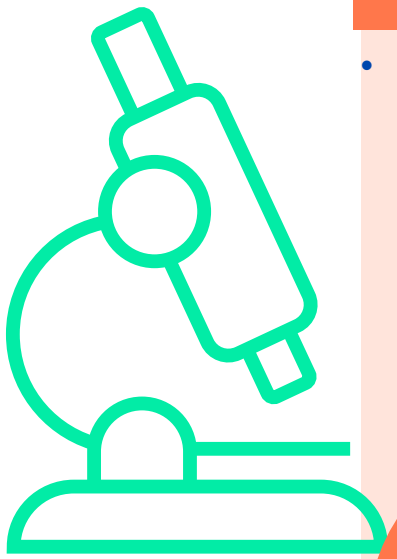
- **Patients are randomized to IVD-guided or standard care**

4. Performance Studies under the IVDR/ ISO 20916 – Good Study Practice for IVDs

For example, national biobank acts, human tissue acts

national requirements notifications or EC approvals for studies using left-over samples.

Key characteristics of qualifying leftover samples include:



Origin:

- Collected originally for routine clinical pathology, screening, standard patient workup, or clinical monitoring.

Independence:

- Samples were collected only as medically needed, with no study-driven changes.

Archival & Biobanks:

- Leftover specimens may come from labs, biobanks, specimen repositories, or commercial vendor

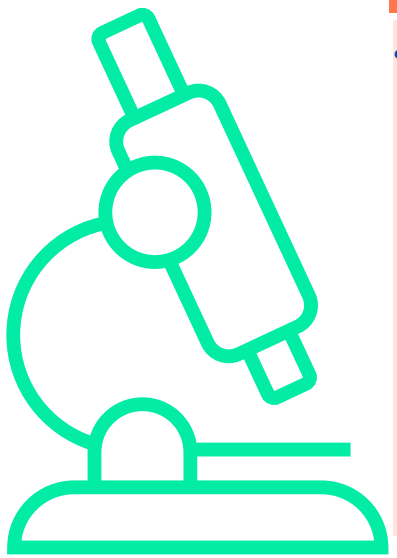
Leftover Status Exempts

- Studies utilizing exclusively leftover samples for non-companion diagnostic IVDs do **not** trigger Article 58(1)(a) (since no invasive sampling was performed solely for the study).
- Provided the test results are not used to guide patient treatment (avoiding Article 58(1)(b)) and no added risks are imposed on subjects (avoiding Article 58(1)(c)), **no competent authority application or EU notification is required under IVDR Chapter VI**

4. Performance Studies under the IVDR/ ISO 20916 – Good Study Practice for IVDs

Co-Development with Pharmaceutical Trials (CTR 536/2014 & IVDR Interoperability)

When a companion diagnostic performance study is embedded within a drug clinical trial governed by the **Clinical Trials Regulation (Regulation (EU) No 536/2014 - CTR)**



Dual Authorization:

- Clinical Trials Information System (CTIS) under CTR 536/2014, CDx studies followIVDR Article 58/66

Interoperability Mandate (Article 69):

- IVDR Article 69 requires the future EUDAMED
- EUDAMED must connect with the CTIS database

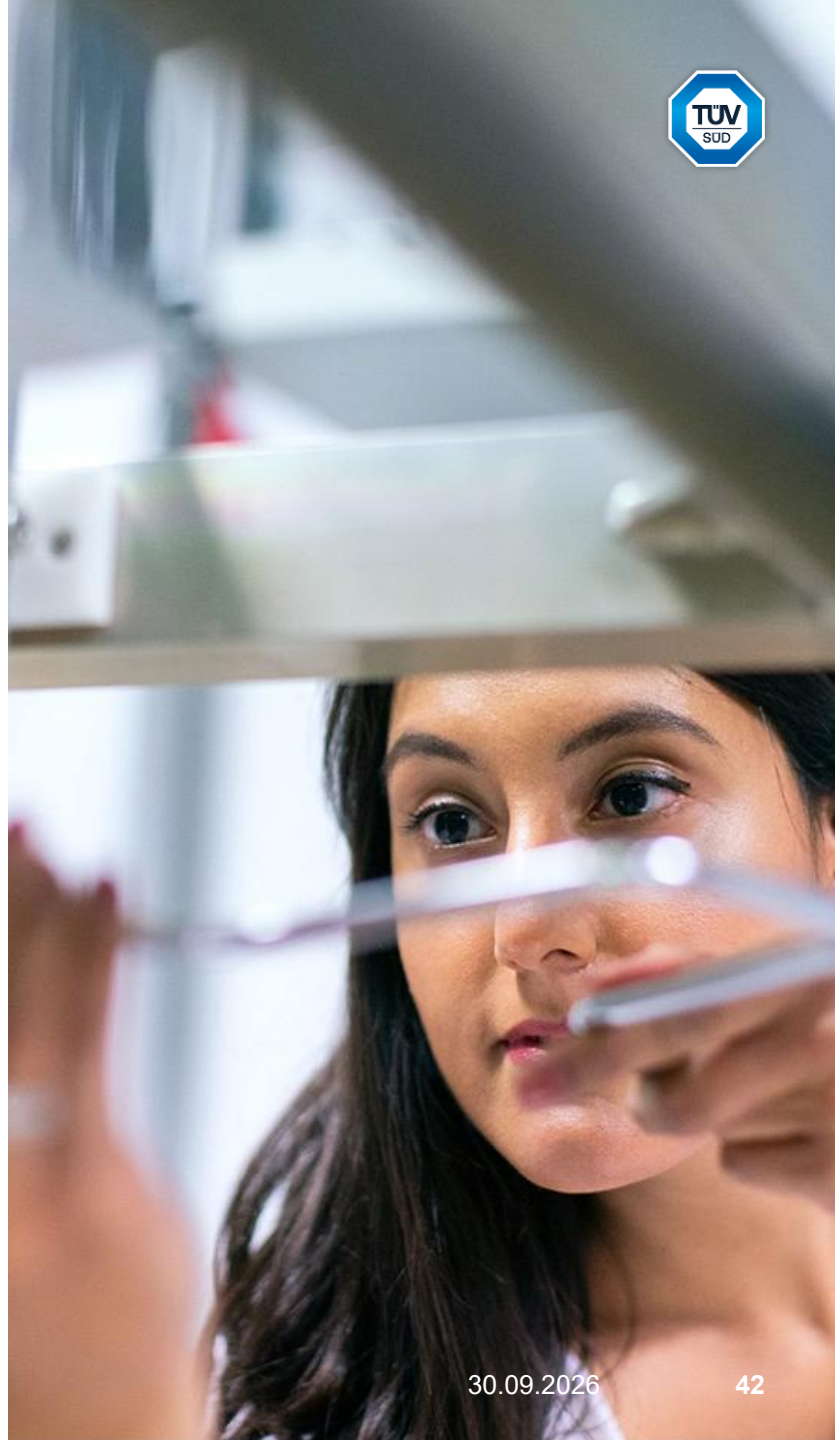
Leftover Exception in Drug Trials:

- Retrospective CDx testing of archived samples requires notification not a full application
- **Article 58(2) vs. Article 66**

For detailed requirements on the notified body consultation file for approved CDx devices, refer to our comprehensive guide on IVDR Companion Diagnostic Consultation Files

8. Typical Findings and Common Mistakes

- Incomplete or inconsistent documentation
- Design ! Design ! Design!
- Deviations from the Clinical Investigation Plan or Performance Study Plan
- Inadequate informed consent documentation
- Insufficient adverse event or safety reporting
- Incomplete source data and poor traceability
- Inadequate training and delegation records
- Weak root-cause analysis and ineffective CAPA



8. Typical Findings and Common Mistakes

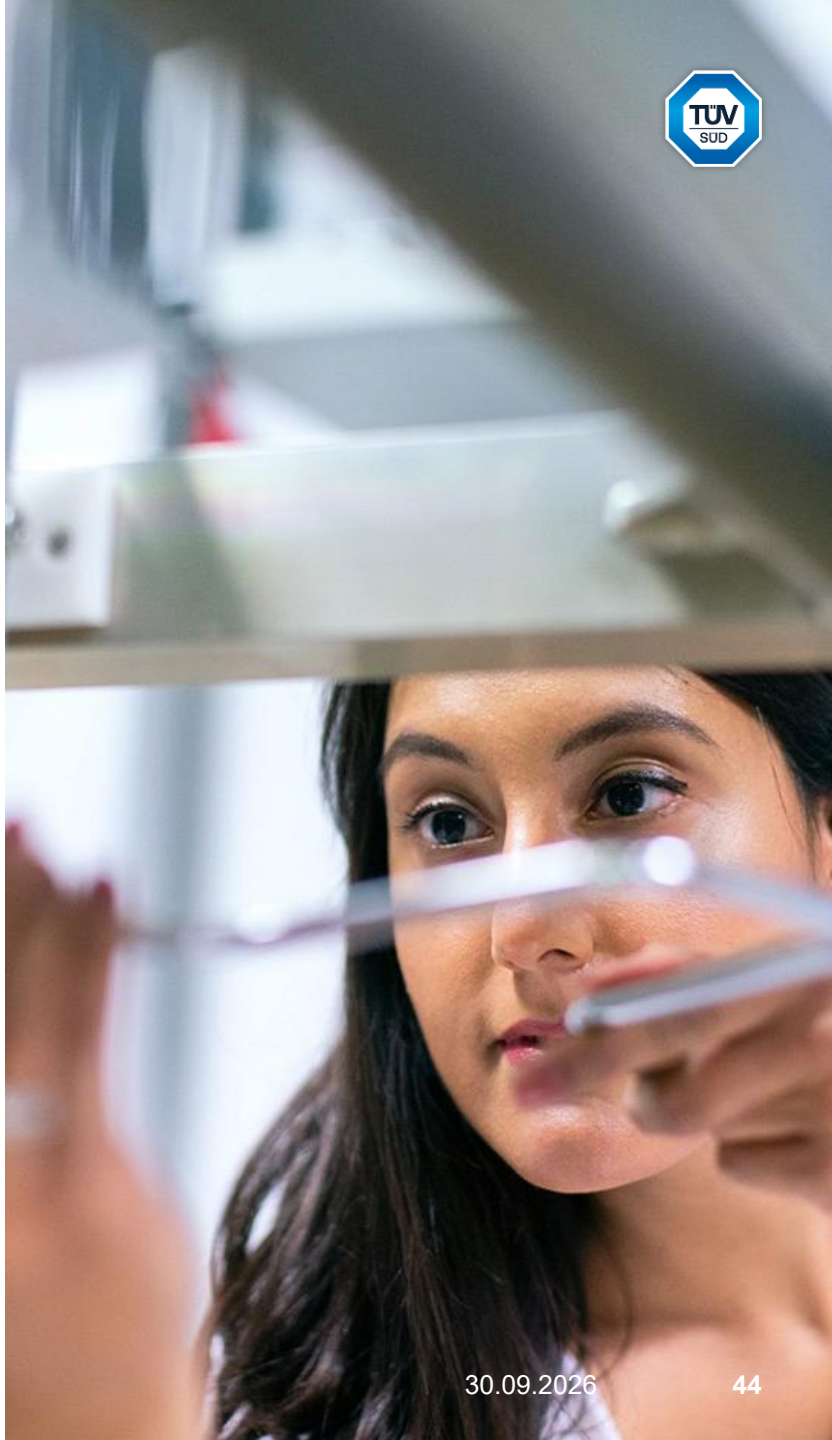
Audit Findings

- **Clinical Investigation**
- LM and distributors were listed as sponsor for a clinical investigation: distributor agreements did not entail any clin invest responsibilities, tasks, etc.,
- Annex XV requirements were not considered for CIP
- Clin Invest documentation was compiled by a CRO. No information about training of CRO personnel of internal procedures
- Advisors/ consultants involved but no supplier qualification/ agreements in place (happens often with medical experts/ physicians)

- **Common PMCF Study Failings**
- •Poorstudy design; too many variables; no control; sample size to small
- •Undefinedor wrong research questions; objectives; study endpoints
- •Wrongstudy population: indications, location
- •Inadequatestatistical justification for sample size
- •Poorly defined or no statistical analysis plan
- •Poorly executed PMCF Evaluation report
- •Device not used according to CIP



8. MedTech GCP Certification Program



MedTech GCP Service Programme (ISO 14155 Standard)



What is ISO 14155?

- Common quality standard for the wellbeing and protection of human subjects in clinical studies
- Standardises design, conduct, recording and reporting of medical device clinical investigations.
- Guidance for clinical research professionals on how to implement Good Clinical Practice (GCP

What is the MedTech GCP Service Programme?

- Evaluates compliance with GCP principles according to ISO 14155 regulations.
- Focuses on clinical quality management (CQM) for clinical investigation design, conduct, recording, and reporting.
- Supports service providers - clinical research organisations, research centres, and investigation

Key considerations

- Certification increases regulators, business partners, medical device users, and patients' confidence and trust.
- International recognition of clinical study results.
- Facilitates the selection process for clinical research organisations / centres / sites

MedTech GCP Service Programme (ISO 14155 Standard) Supply - Chain in Clinical Research with Medical Devices

Covered by Voluntary Clinical QMS-Certification

Responsible Institutions	Manufacturer Medical Device	Clinical Research Organisation	Clinical Research Center	Investigation Site
Involved Personal	**Sponsor** depend on contractual agreements Team of Specialists		**Sponsor** if Investigator initiated Study Team of Specialists	

MedTech GCP Service Programme (ISO 14155 Standard)

Value of MedTech GCP program for clinical research organisations/institutions

Credibility and Trust



- **Certified confirmation** of core competencies
- Enhancing trust and credibility among manufacturers and suppliers/vendors; recognition for high-quality performance
- Reliability of trial results

Global Access to Clinical Investigations



- ISO 14155 is a globally recognized standard

  global market entry
- Competition on a global level
- Face the challenges of the future:

  Regulation (EU) 2017/745 and several MDCG documents require **compliance with ISO 14155** (correspondence between Annex XV of the MDR and various clauses of ISO 14155)

Reduction of Financial Risks



- Efficient Clinical Quality Management system
- **Effective** resource planning and **allocation of financial resources**
- Reduction of unforeseen events through standard operating procedures

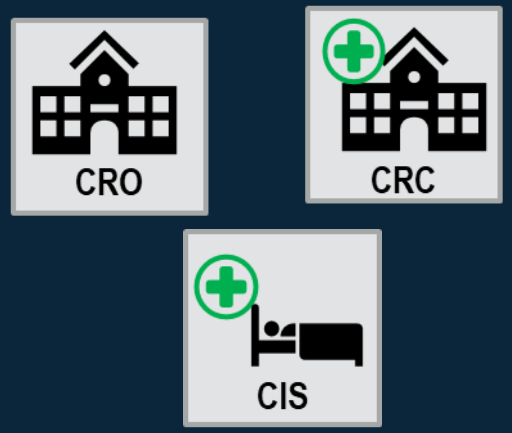
Clinical Resources & Patient Recruitment

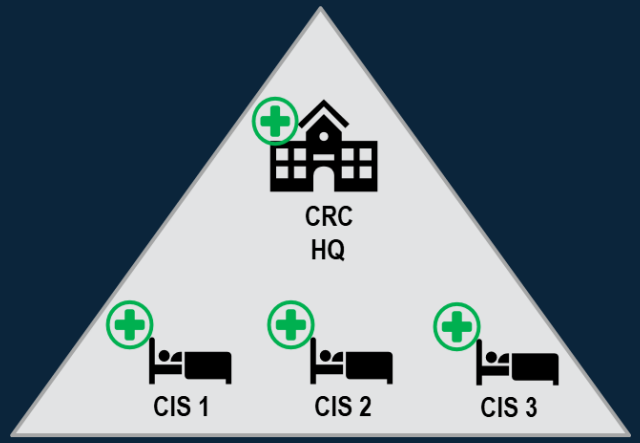


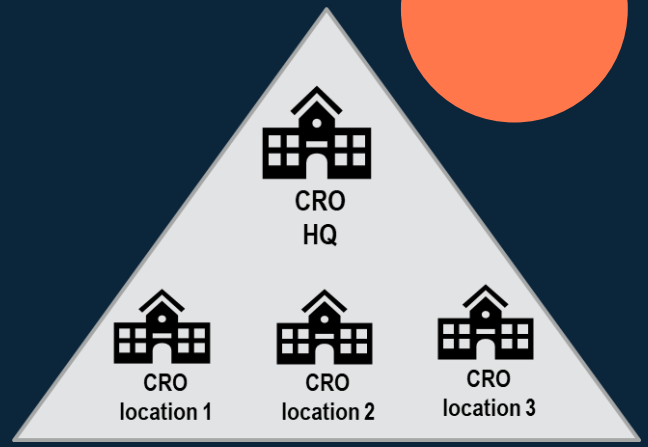
- Certified capability of resources to conduct or support clinical investigations
- Certified capability to ensure patient safety and high ethical standards
- **Increase** trust of **volunteers** to participate in clinical investigations

Medtech GCP Audit Scheme

The audits can be conducted as **single-location** or **multi-site audits**







- **Multi-site audits** are applicable to CROs and CRCs where
  - activities subject to audit are carried out in different facilities/sites/CISs and
  - under the authority and control of a lead facility/site/headquarters.
  - This approach is only possible if the CRO or CRC has an integrated and centrally controlled QMS

- In order to effectively coordinate the audit activities a **multi-site audit program including sampling** shall worked out client specific .

Danke

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