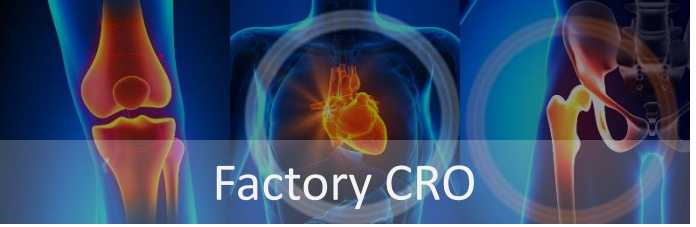
Factory CRO

DCRF Jaarcongres, 26 september 2018

MDR 2020 - De impact op onderzoek met medische hulpmiddelen

Klinische evaluatie en klinische studies

Niels van Tienen



Bio

Current role

- Director Clinical Operations, Factory-CRO for Medical Devices

Training

- Academie Lichamelijke Opvoeding, Tilburg
- Bewegingswetenschappen, Maastricht

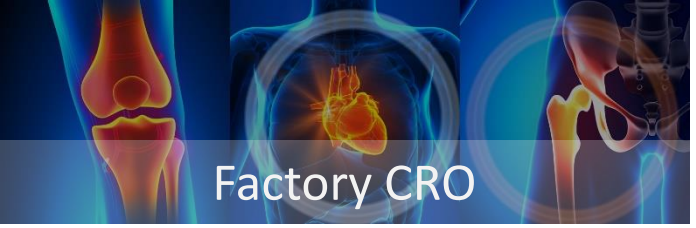
Work experience

- Bewegingsonderwijs ZMLK, Hilversum
- CRA, Medtronic, Arnhem, Minneapolis
- CRA, PM, Factory-CRO for Medical Devices, Bilthoven, Princeton

Responsibilities

- Leading clinical operations team
- Trainer procedures, rules and regulations (in-house and outdoors)
- HR

https://www.linkedin.com/in/nielsvantienen/



CRO

CRO

Service provider

QMS
ISO13485:2016
ISO14155:2011

Audited by NB

Medical writing
Data management
Clinical operations
Regulatory consultancy
Reimbursement

Medical writing

Clinical evaluation
- CER
- State of the art

CIP development

PMCF plan

Data management

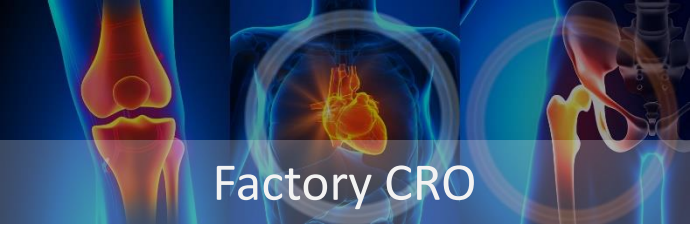
Design databases
Validate data from clinic

Tables and listings

Clinical operations

Clinical investigations
- FIM
- Feasibility
- Pivotal
- PMCF

From CIP to clinic
- GCP
- Training investigators



From MDD to MDR

3 major directives

- Active Implantable Medical Device Directive (90/385/EEC)
- Medical Device Directive (93/42/EEC)
- Amending Directive 2007/47/EC
- In Vitro Diagnostic (IVD) Medical Device Directive (98/79/EEC)

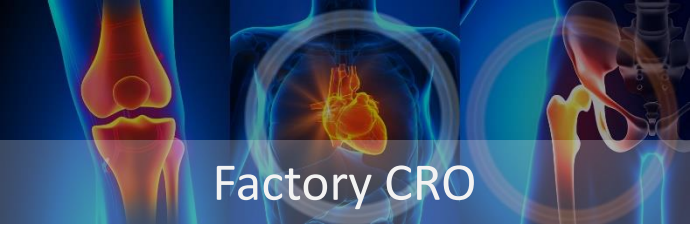
Medical Device Regulation (EU 2017/745)

- Replaces AIMD, MDD
- Amends
  1. Directive 2001/83/EC Regulation (EC) No 178/2002 (Food safety)
  2. Directive 2001/83/EC Regulation (EC) No 1223/2009 (Cosmetic Products)
  3. Directive 2001/83/EC (Medicinal products for human use)

In Vitro Diagnostic Medical Device Regulation (EU 2017/746)

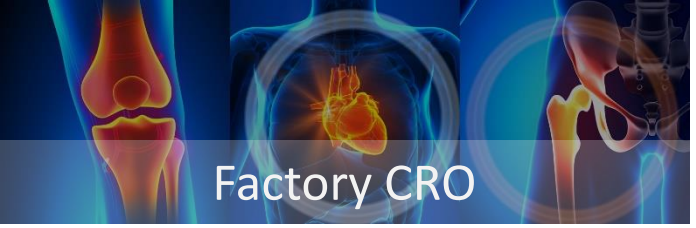
- Replaces IVDD

- Decision 2010/227/EU (Commission decision on EUDAMED) remain in force and until Eudamed becomes fully functional
- No transposition
- MEDDEV guidance documents in body text



Timelines

May 5, 2017	2017/745 and 2017/746 published May 5, 2017 in the Official Journal of the European Union (OJEU)
May 26, 2017	Entry into force
May 26, 2020	MDR date of application
May 26, 2022	IVDR date of application
May 26, 2024	AIMD, MDD and IVDD certificates become void; after this date, no more devices may be placed on the European market under these certificates
May 26, 2025	After this date, no devices may be put into service in Europe using MDD, AIMD or IVDD certificates



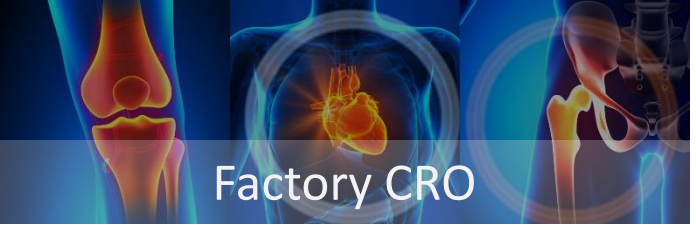
Major changes MDR

Concerning clinical investigations and clinical evaluation

- Reinforcement of the rules on clinical evidence
- Reassessment of devices of all devices, even when on market
- Life cycle approach
- Active approach
- EUDAMED

- Implant card

- Source https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en



Reinforcement of the rules on clinical evidence

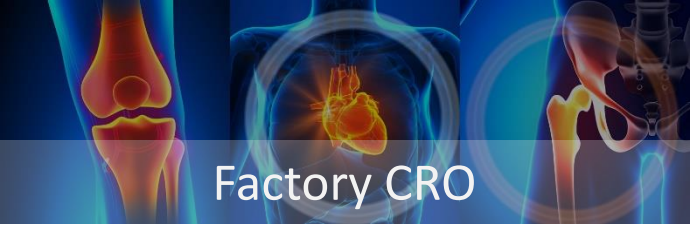
From directive to regulation

Guidance documents in body text

- MEDDEV 2.7/1 rev 4, Clinical Evaluation
- MEDDEV 2.7/4, Guidance on Clinical Investigations
- MEDDEV 2.7/3, Clinical Investigations - SAE reporting
- MEDDEV 2.12, Post Market Clinical Follow-up

Stricter requirements on clinical evidence

Amending Directive 2007/47/EC	2010	Demonstration of conformity with ER includes a Clinical Evaluation in accordance with Annex X
MEDDEV 2.7/4	June 2016	Demonstration of conformity with ER on data from equivalent devices when **clinical, technical, biological** equivalence justified, access to technical file
MDR EU 2017/745	May 2020	Demonstration of conformity with SPR on data from equivalent devices when full access to technical documentation, contract in place

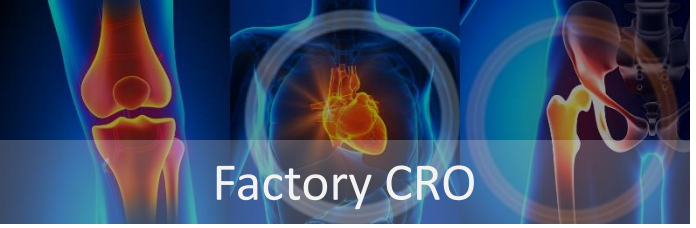


Reassessment of all devices

Clinical evaluation

- Demonstration of conformity with the general safety and performance requirements shall include a clinical evaluation in accordance with Article 61

- Clinical evaluation means a systematic and planned process to continuously generate, collect, analyse and assess 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



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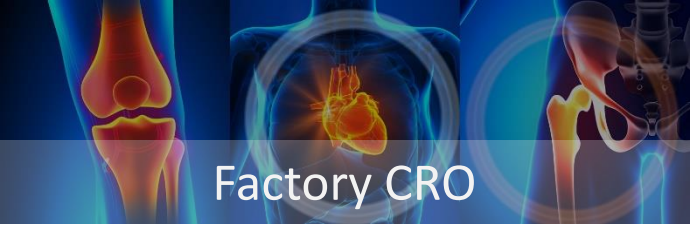


Pre-market clinical investigations

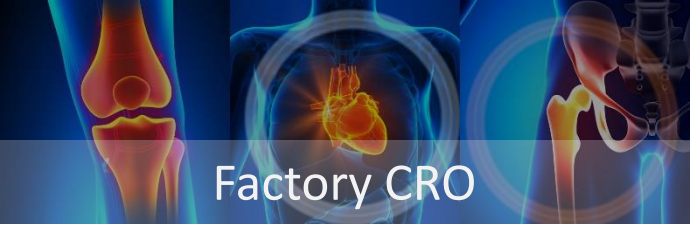
MDR, Chapter VI, Article 62, 1.

‘Clinical investigations shall be designed, authorised, conducted, recorded and reported […], for one or more of the following purposes:

(a) to establish and verify that, under normal conditions of use, a device is designed, manufactured and packaged in such a way that it is suitable for one or more of the specific purposes listed in point (1) of Article 2, and **achieves the performance intended as specified by its manufacturer**; […]

(b) to establish and verify the **clinical benefits** of a device as specified by its manufacturer;

(c) to establish and verify the **clinical safety** of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device’



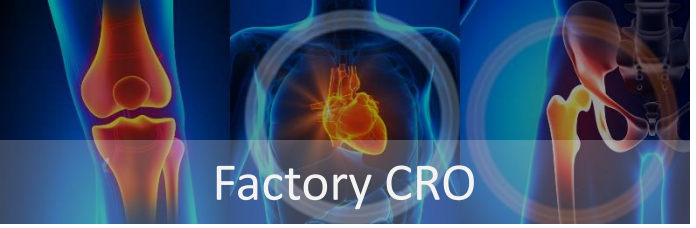
Pre-market clinical investigation

MDR, Chapter VI, Article 61(4).

In the case of **implantable devices and class III devices, clinical investigations** shall be performed, except if:

- the device has been designed by **modifications** of a device already marketed by the same manufacturer,
- the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, in accordance with Section 3 of Annex XIV and this demonstration has been endorsed by the notified body, and
- the **clinical evaluation** of the marketed device is **sufficient** to demonstrate conformity of the modified device with the relevant safety and performance requirements.

In this case, the notified body shall check that the PMCF plan is appropriate **and includes post market studies** to demonstrate the safety and performance of the device.



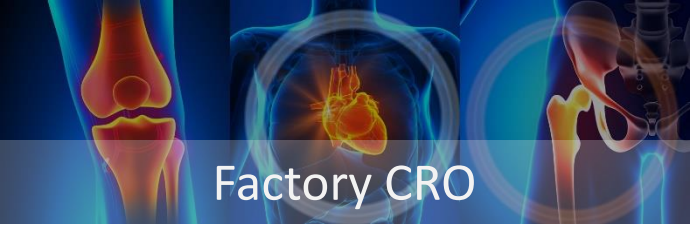
Reassessment of all devices

MDR, Chapter VI, Article 61(6).

The requirement to perform clinical investigations pursuant to paragraph 4 shall not apply to implantable devices and class III devices:

a) which have been lawfully placed on the market or put into service in accordance with Directive 90/385/EEC or Directive 93/42/EEC and for which the clinical evaluation:
   - is based on sufficient clinical data, and
   - is in compliance with the relevant product-specific Common Specifications for the clinical evaluation of that kind of device, where such a CS is available; or

b) that are sutures, staples, dental fillings, dental braces, tooth 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 Specifications, where such a Common Specification is available.



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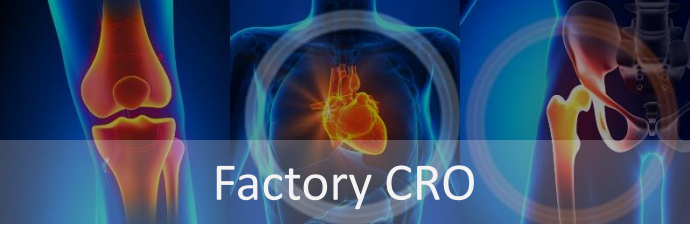
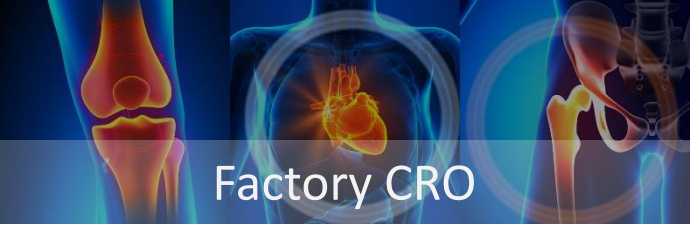


Lifecycle approach

The lifecycle activities associated with clinical evidence for a medical device include

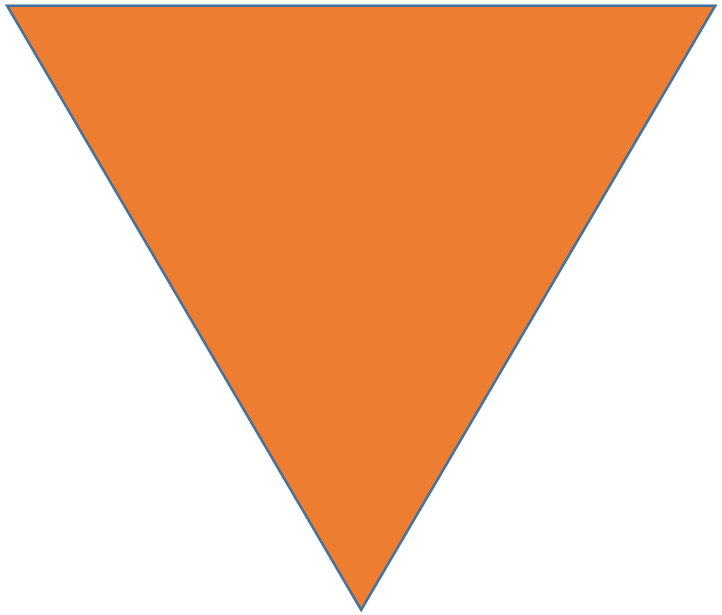
- Establishing clinical evidence through pre-market clinical evaluations or clinical investigations
- Preparing and maintaining clinical evaluation reports (CERs)
- Planning and conducting post-market clinical follow-up (PMCF), or justification why not applicable



Life cycle approach – Interaction

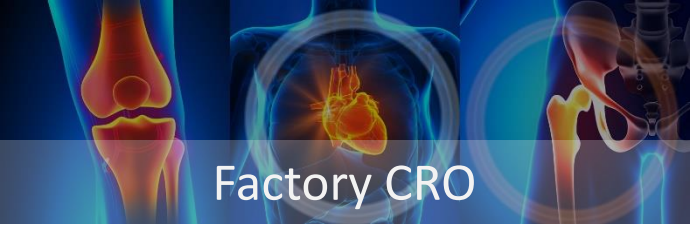
Risk Management

Clinical Evaluation



Post-Market Surveillance / Post-Market Clinical Follow-up

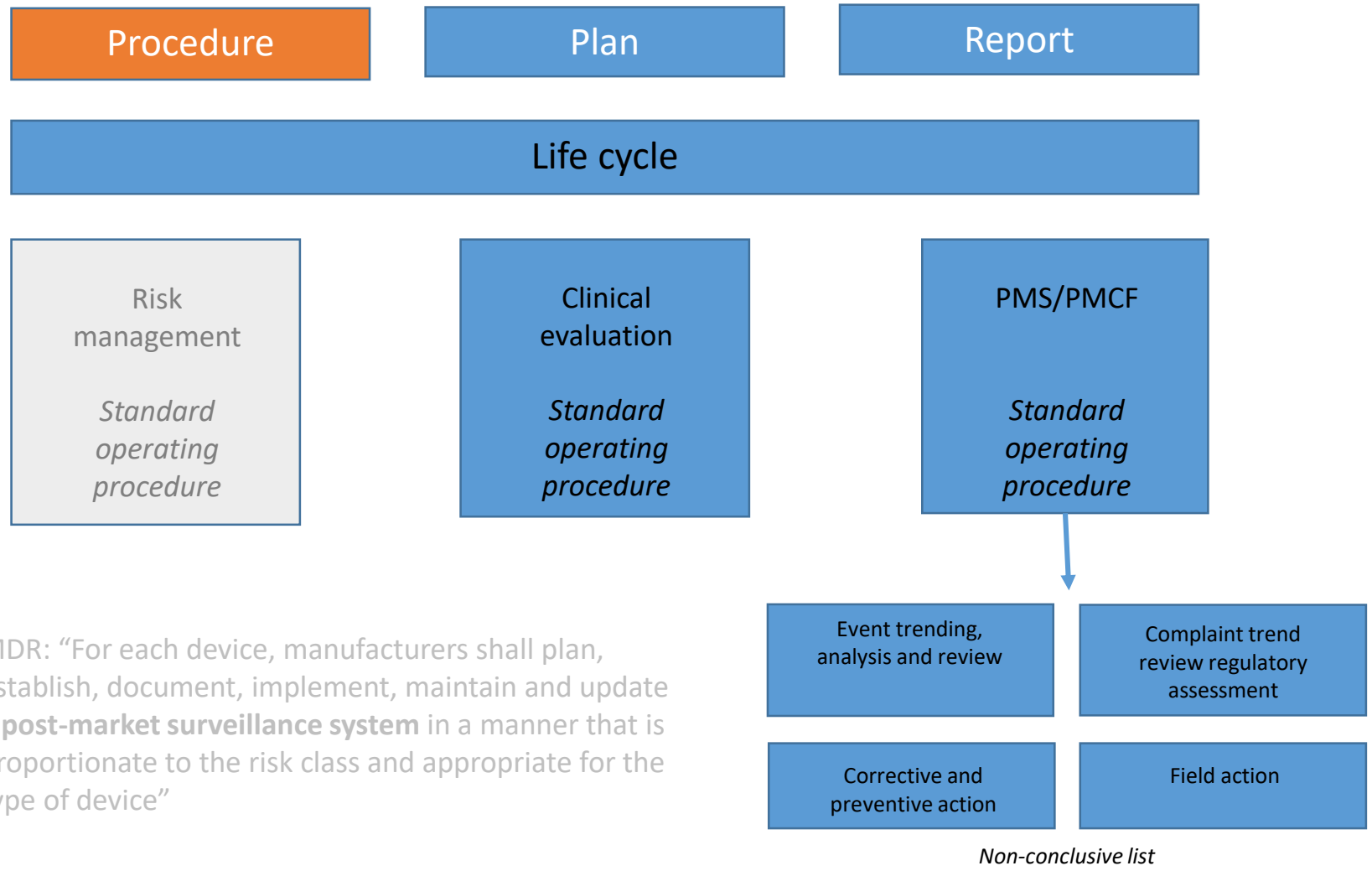
- Procedure
- Plan
- Report



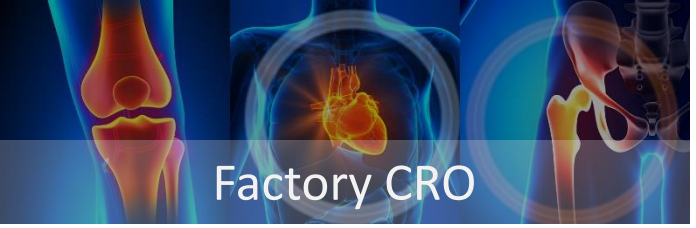
Life cycle approach – Procedure overview

A standard operating procedure ensures that you use the same methodology for all clinical evaluations or PMS/PMCF activities that you perform.

Not only between different devices, but also, for example, with each update that you have to implement.



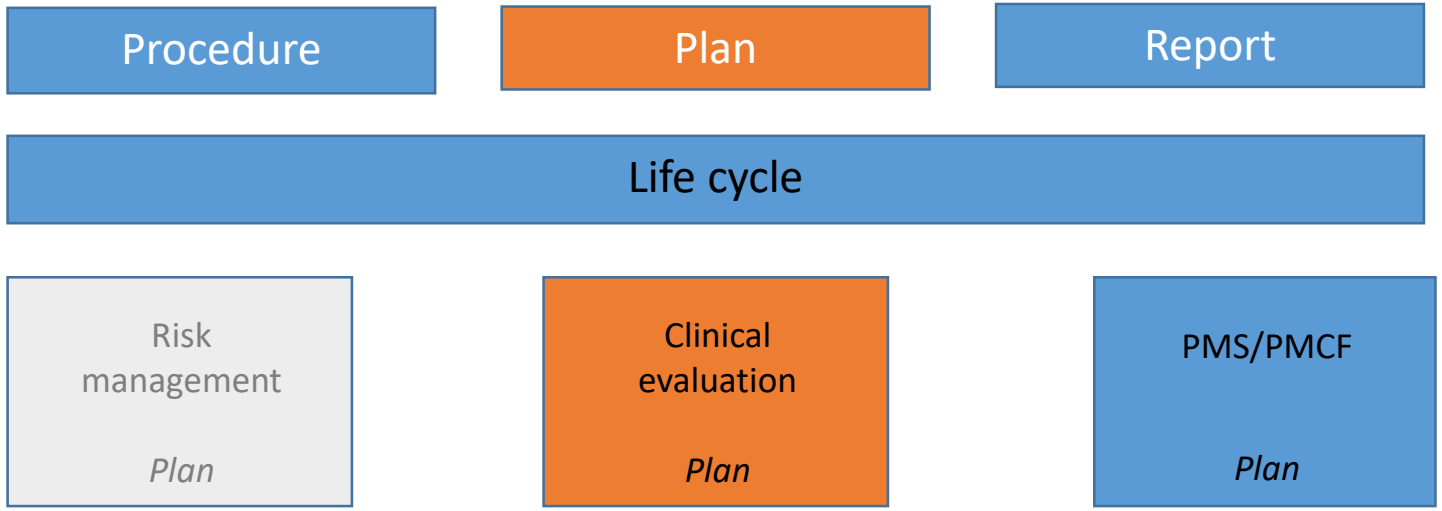
MDR: "For each device, manufacturers shall plan, establish, document, implement, maintain and update a **post-market surveillance system** in a manner that is proportionate to the risk class and appropriate for the type of device"



Life cycle approach – Plan overview

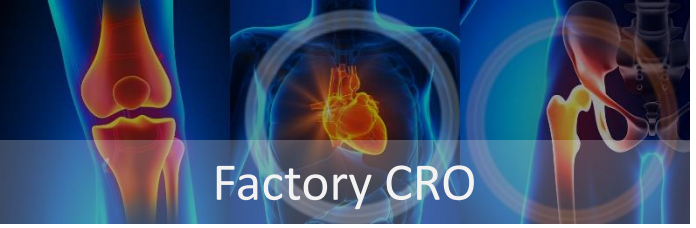
A plan allows to you to think your actions through from the beginning.

How are you going to evaluate your device? When are you going to do this? Which information will you take in to account? Is there any specific information that you are looking for?



Clinical evaluation plan

- Decide which **device** you are going to evaluate
- Decide which **indication** you are going to evaluate
- Make an inventory of the clinical data you **have available**
- Decide whether you want to base your evaluation on **equivalent devices**
- Decide which clinical data you are going **to collect**
- Outline responsibilities and which **team of evaluators and/or reviews** are qualified to conduct the clinical evaluation; outline timelines for reporting



Life cycle approach – Active methods

A plan allows to you to think your actions through from the beginning.

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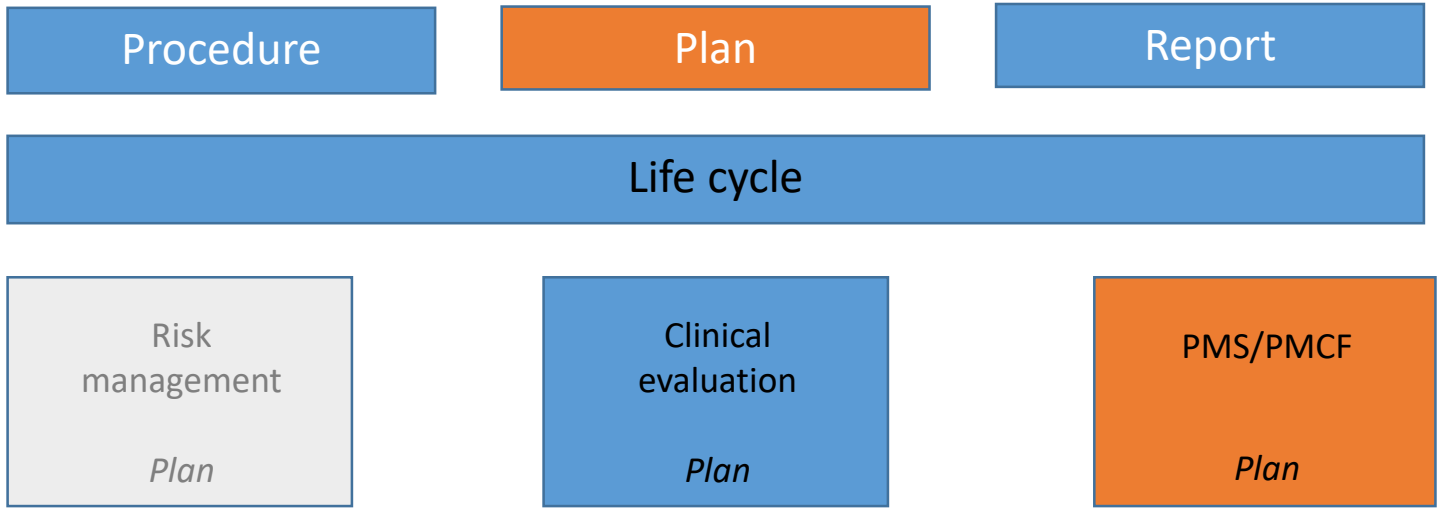
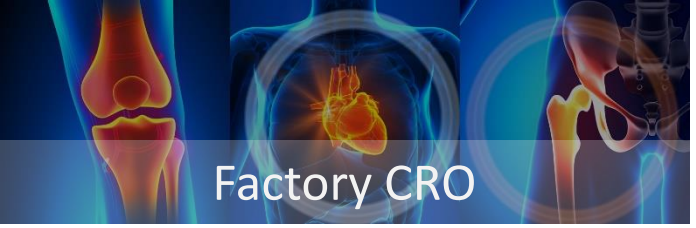


PMS Plan

- Outline which **passive** methods for post-market data collection you are going to conduct
- May include MAUDE database review, event/complaint trending
- Refer to PMCF Plan for active methods

PMCF Plan

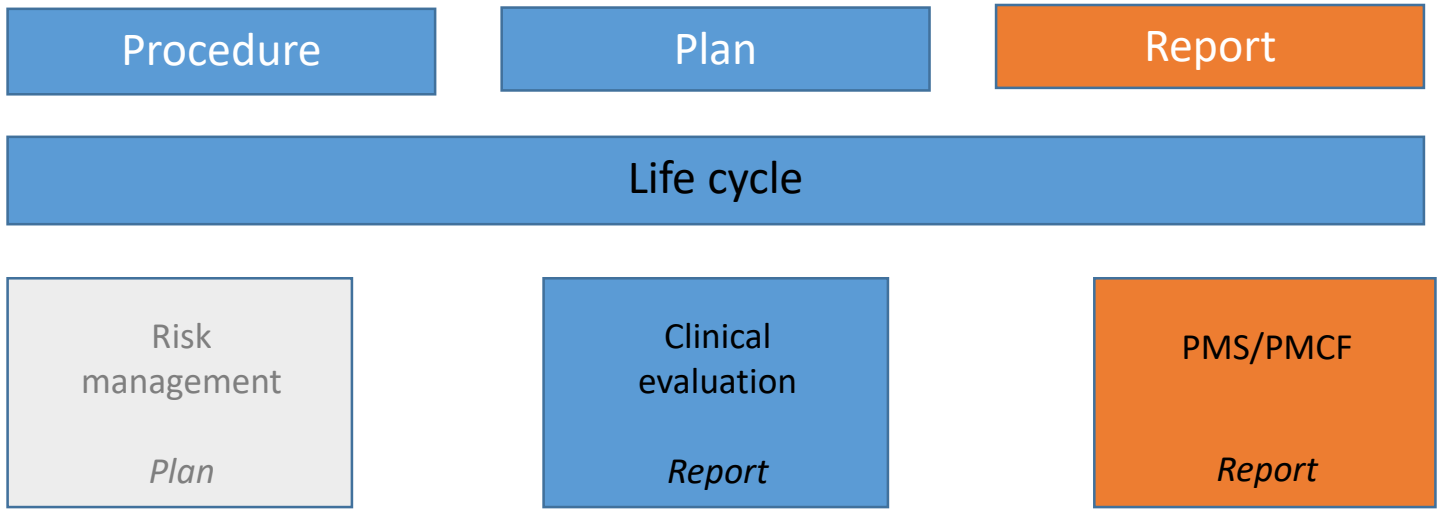
- Outline which **active** methods for post-market data collection you are going to conduct
- May include focus group meetings, customer surveys, literature reviews, user reaction during training, PMCF studies



Life cycle approach – Reports overview

In the reports you periodically create overviews of the data, and associated clinical evidence, that you have on your device.

Which information did you take into account? What did you find there? Did new questions arise, or have questions been answered? Are there any safety risks identified that you were not aware of?

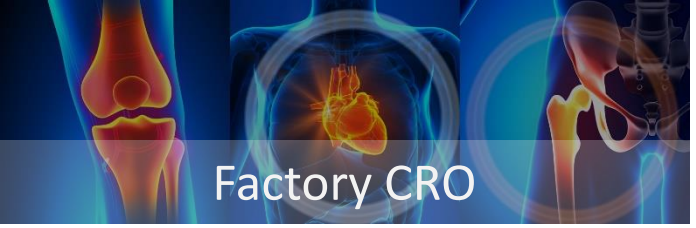


PMS Report / PSUR

- Describes outcomes of passive methods for post-market data collection
- May include vigilance reporting, field safety actions, corrective and preventive actions, recalls

PMCF Report

- May include data from literature reviews, customer surveys, PMCF studies



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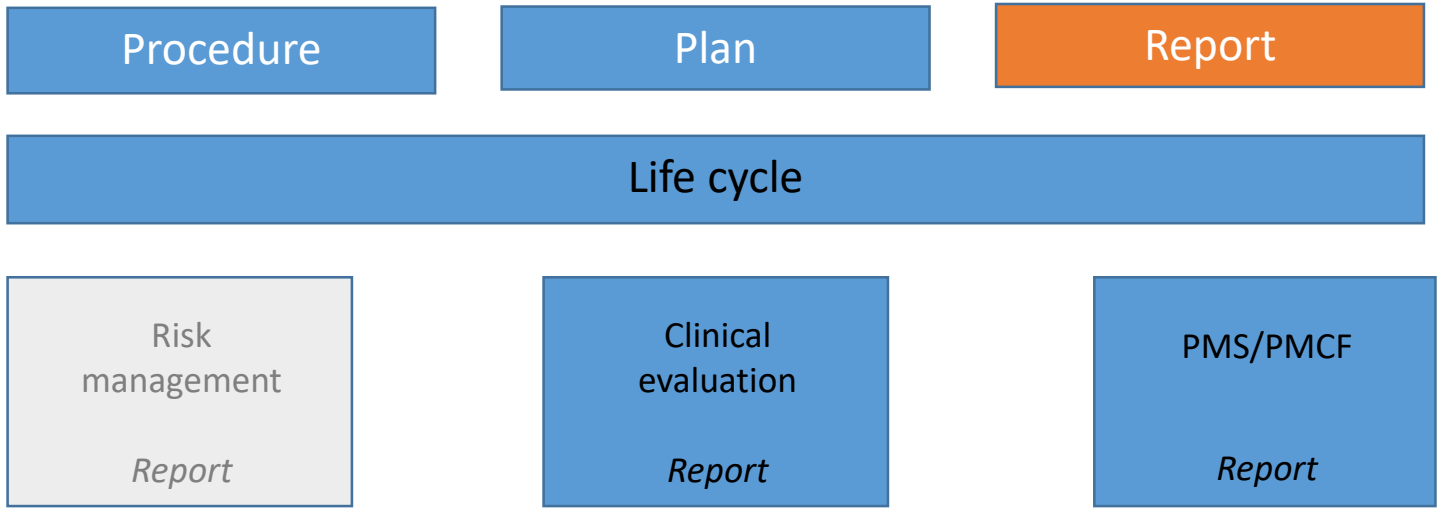
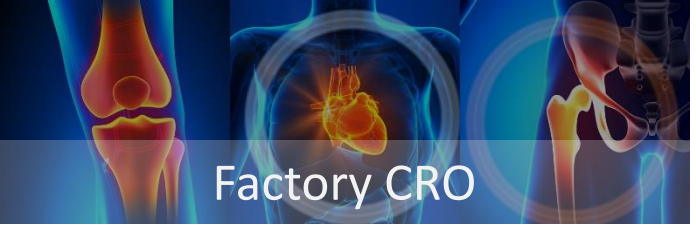


May include your 'summary of safety and clinical performance' (SS&CP)

'PMS report' for Class 1 devices.

'Periodic safety update report' (PSUR) for Class IIa, IIb and III devices.



PMCF

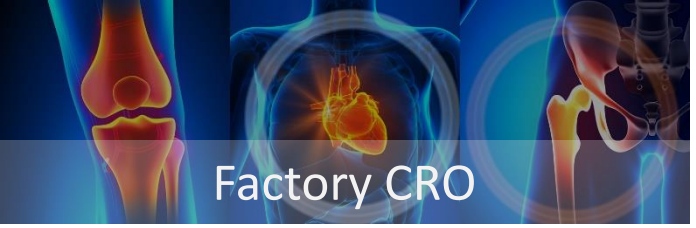
Annex XIV **POST-MARKET CLINICAL FOLLOW-UP**

When conducting PMCF, the manufacturer shall **proactively** collect and evaluate **clinical data** from the use in or on humans of a device which bears the CE marking and is placed on the market [..], with the aim of **confirming the safety and performance throughout the expected lifetime of the device**, of ensuring the continued acceptability of identified risks and of detecting emerging risks on the basis of factual evidence.

Clinical Data means information concerning safety and performance that is generated from the use of a device and is sourced from clinically relevant information from post-market surveillance, in particular the PMCF

PMS and PMCF studies are **not new concepts** in European medical device compliance.

- **Perform a clinical data gap analysis** with respect to the new MDR.
- Start PMCF investigations **now**, while devices still CE Marked under the current MDD to prepare certification under the new MDR.
- Design studies with the new MDR requirements in mind, to enable acceptability of these data for certification under the MDR.



Data Collection Methods

Passive Methods:

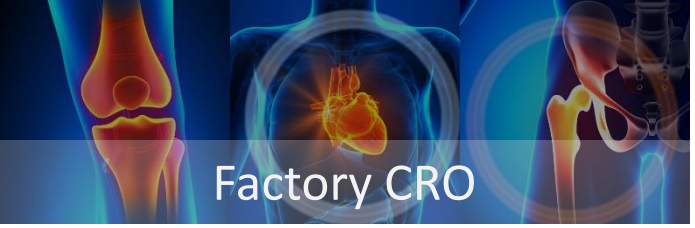
- Customer complaints and warranty claims
- User feedback other than complaints, either directed to manufacturer or via sales force
- The media
- Other bodies (CA/Member State)
- Maintenance/service reports
- Experience with similar devices made by the same or different manufacturer

Active Methods (PMCF):

- Focus groups
- Customer surveys
- Literature reviews
- Device tracking/implant registries
- User reaction during training programs
- In-house testing
- Retrieval studies on explants or trade-ins
- Fracture analysis

Fixed

Variable



Level of Evidence PMCF Methods

Low **Medium** **High**

5. Post-Market Clinical Investigation

4. Post-Market Registry

3. Literature review

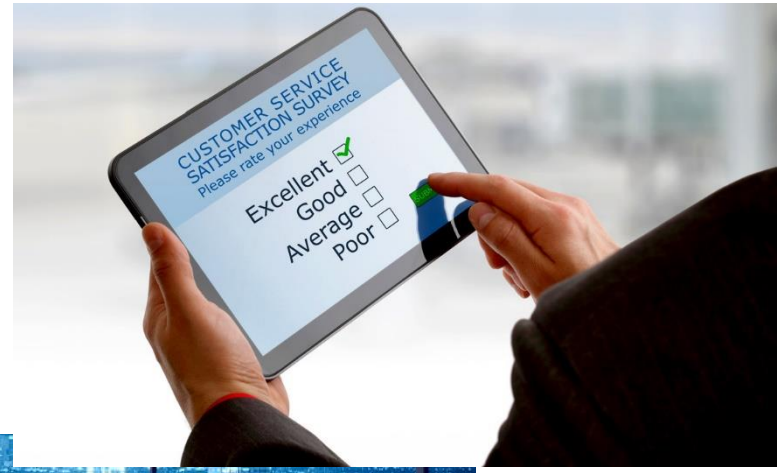
2. Learn and Improve

1. User Feedback

User Experience

Examples:

- Focus groups (e.g. advisory board meeting, scientific commission)
- Customer survey
- User reaction during training sessions



Regulatory requirements: -

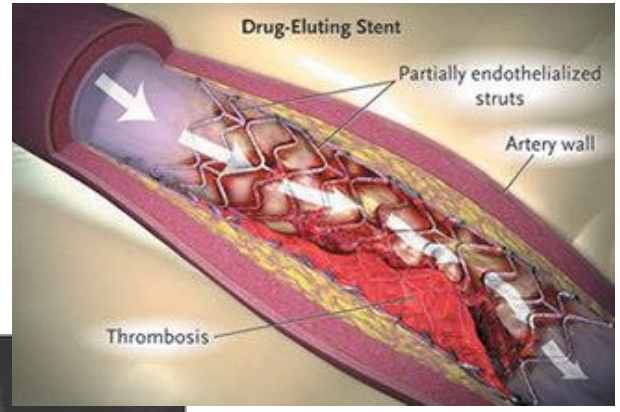
Pros and cons:

+ Low effort
+ Low costs
+ Fast input
- Low level evidence

Learn and Improve

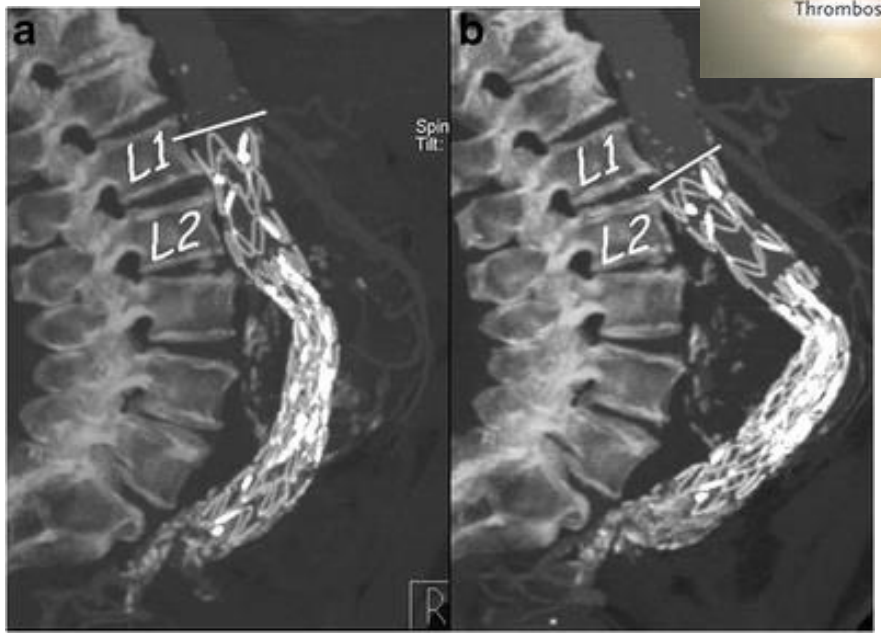
Examples:

- In-house testing (e.g. additional pre-clinical testing, translational studies)
- Retrieval studies on explants or trade-ins (e.g. failures analysis)
- Fracture analysis (i.e. process optimization)



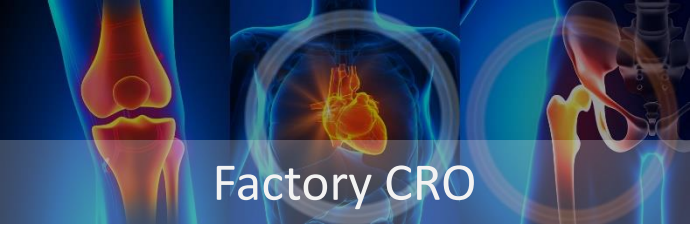
Regulatory requirements:

- Depending on involvement of subject



Pros and cons:

+ Input for higher level evidence
+ Good for “learning” (e.g. risks)
- Low level evidence



Post-Market Registry

Examples

Sponsor

Third party registry

- NHS national joint registry
- Dutch Spine Surgery Registry

Data

Standard of care data

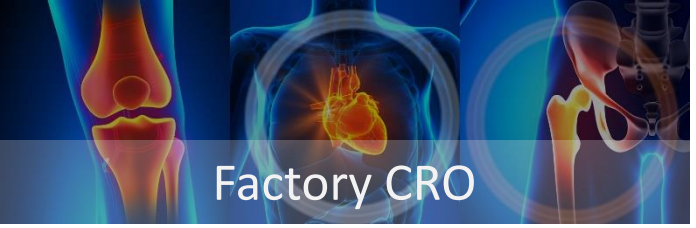
Real-world experience

Regulatory requirements

Pseudonymization → Informed consent

Anonymization → No informed consent

Sponsor	Third party
Effort depends on registry design	Effort depends on registry design
Higher costs	Lower costs
Full access to data	Less control over data
Quality determined by sponsor	Quality depends on organization
Less regulatory requirements compared to PMCF study	



Post-Market Clinical Investigation

PMCF Study:

1. Investigator
2. Sponsor

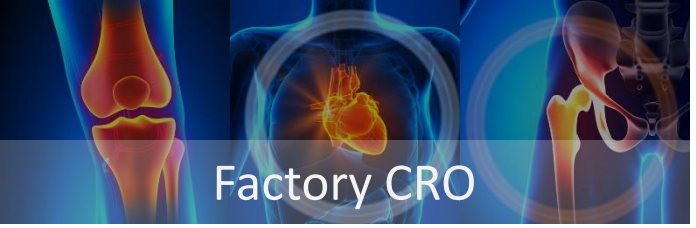
Investigator-initiated	Sponsor-initiated
Low effort, but less control	Higher effort
Low costs	Higher costs
Less control over study design and data	More control over study design and data
Lower quality	Higher quality

PMCF Investigation (MDR, article 74):

- Devices bearing CE marking
- Extension of Pre-Market Clinical Investigation

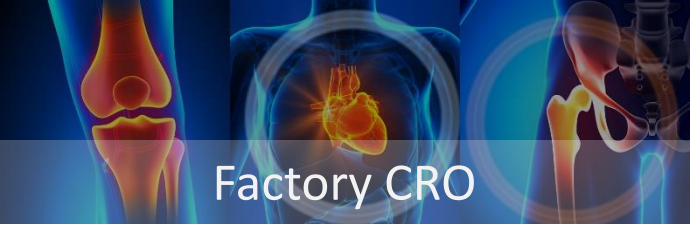
Regulatory requirements:

- Common GCP standard (e.g. ISO 14155)



Examples Clinical Investigations

Status	Development stage	Design	Examples	Burden
No CE mark / new indication	Pilot study Or Pivotal study	Exploratory Or Confirmatory	First-in-Man study Or (Early) Feasibility study	Interventional to subject
CE mark	Post-market study	Confirmatory Or Observational	Post-market study Or Registry study	Interventional to subject Or Non-Interventional to subject



ISO14155 in 30 seconds

Standard - choice
No certification – audited by third party

Patient safety
Data integrity

Consent patients
IP accountability
Report SAEs
Ensure training and qualification

Comply with the CIP

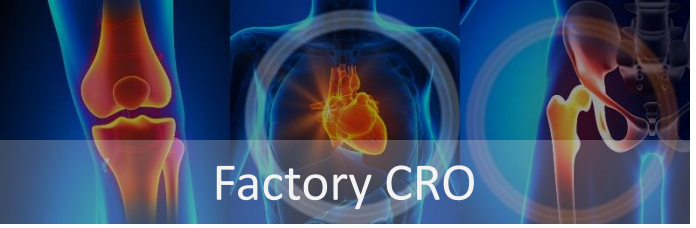
INTERNATIONAL STANDARD

ISO 14155

Second edition
2011-02-01

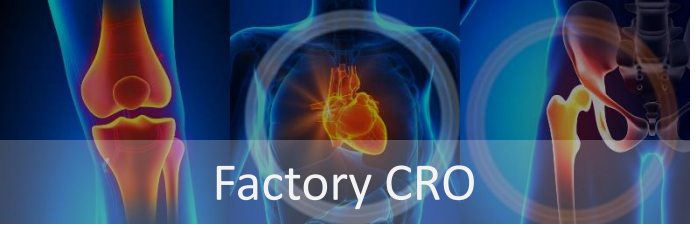
Clinical investigation of medical devices for human subjects — Good clinical practice

Investigation clinique des dispositifs médicaux pour sujets humains — Bonnes pratiques cliniques



Applicability ISO14155:2011 standard

Lifetime	CE Mark	Stage	Study type	Not required when justified
Device development	N	Pilot, exploratory	FIM, early feasibility	Pre-specification of a statistical hypothesis
Design freeze	N	Pivotal, confirmatory	Feasibility	
Post marketing	Y	Confirmatory, interventional	Post Marketing Study	Device accountability Study-specific Labelling Investigator Brochure (IB) Reporting to regulatory authorities
Post marketing	Y	Observational, non-interventional	Registry	Device accountability Study-specific Labelling IB Reporting to regulatory authorities ICF if waived by EC, only personal data protection requirements CV of the investigation site team



EUDAMED

EU database on medical devices

- Improved transparency
- Unique Device Identification

Improved coordination between EU countries in the fields of vigilance and market surveillance

Living picture of the lifecycle of all products being available on the EU market

Parts publicly available

- SSCP Class III and implantable devices

EU-wide coordinated procedure for authorization of multi-center clinical investigations