Total Lifecycle Assessment - New Devices, Post Market Surveillance, Device iterations and Recertification

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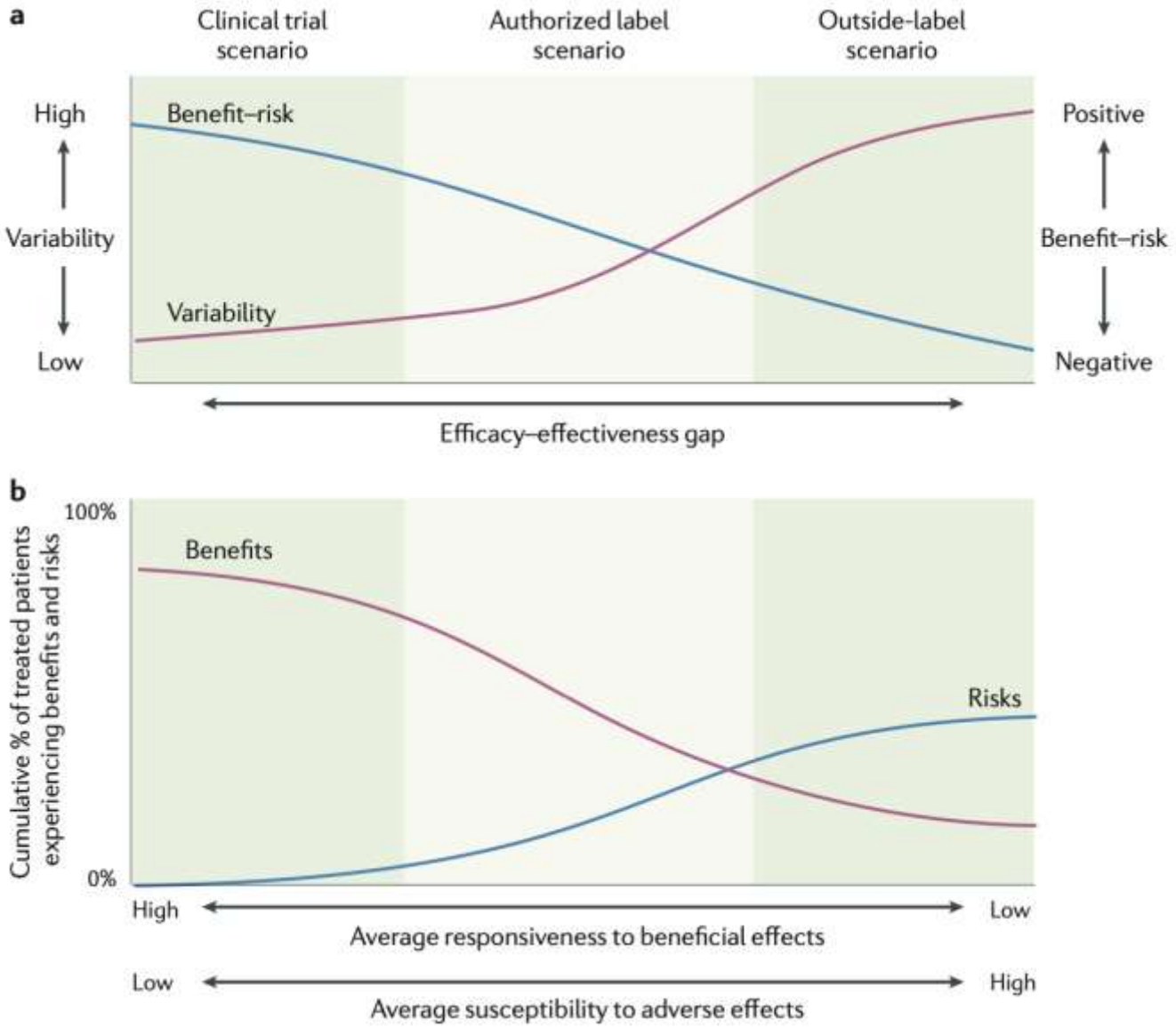
ESC
European Society of Cardiology

CLINICAL TRIAL SCENARIO VS. OUTSIDE-LABEL SCENARIO



- In the context of **regulatory clinical trials**, **variability is kept to a minimum** by enforcement treatment conditions and narrow selection criteria, which aim to restrict patient population to high-responders and good tolerators

- Treatment eligibility is **less constrained in the authorized label scenario** and even less so after it a drug or device comes to the market

- **As variability increases, average risk/benefit ratio progressively decreases**

Eichler HG et al., Nat Rev Drug Discov. 2011 Jul 1;10(7):495-506

The Example of First-Generation DES

Study	Stent	Sample size	Follow-up	Stent thrombosis
RAVEL (2002)	Cypher	**238**	1 year	No episodes overall
SIRIUS (2003)	Cypher	**1058**	270 days	0.4% vs. 0.8% with standard stent
TAXUS IV (2004)	Taxus	**1314**	9 months	0.6% vs. 0.8% with standard stent
TAXUS V (2005)	Taxus	**1156**	9 months	0.7% in both groups

- **Cypher**: CE mark in April 2002, FDA approval April 2003
- **Taxus**: CE mark in January 2003, FDA approval March 2004

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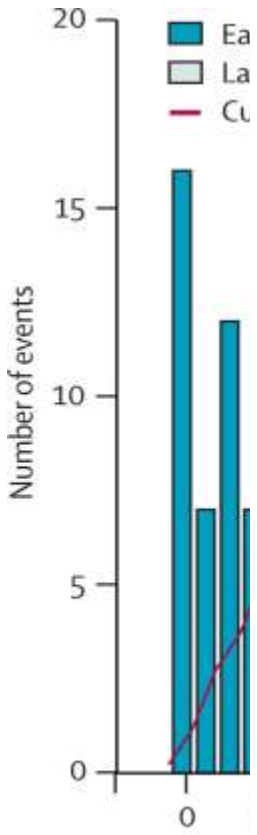
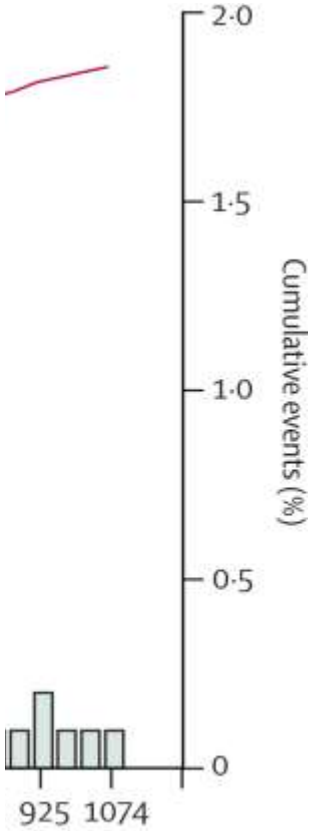
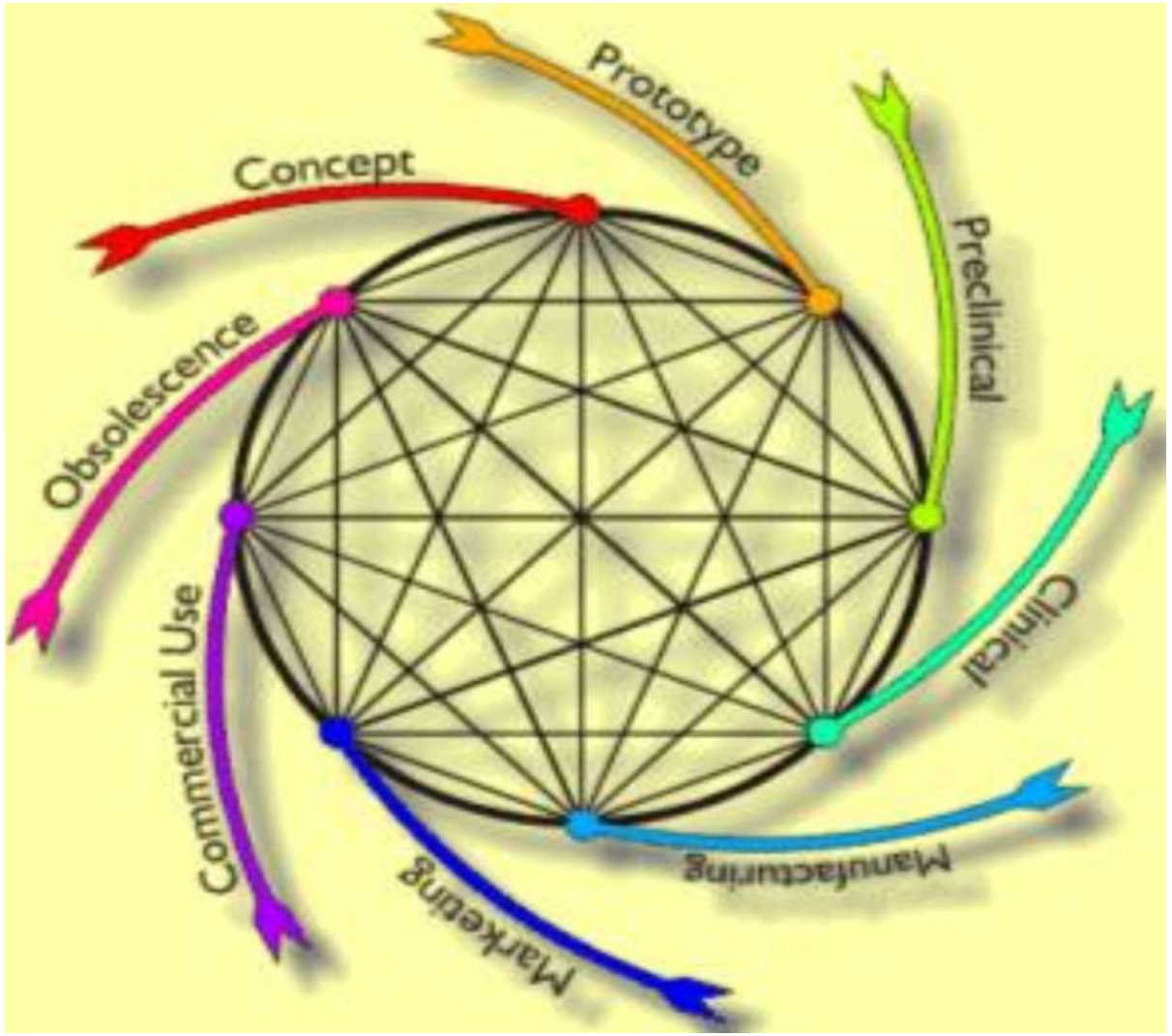




The Importance of Total Lifecycle Assessment



- **Pre-market device trials** face intrinsic issues related to small sample size and limited follow-up, which **do not allow to assess rare and late adverse events**

- **Post-market surveillance is pivotal** to assess real-world device performance, long-term safety, and effectiveness in larger patient populations

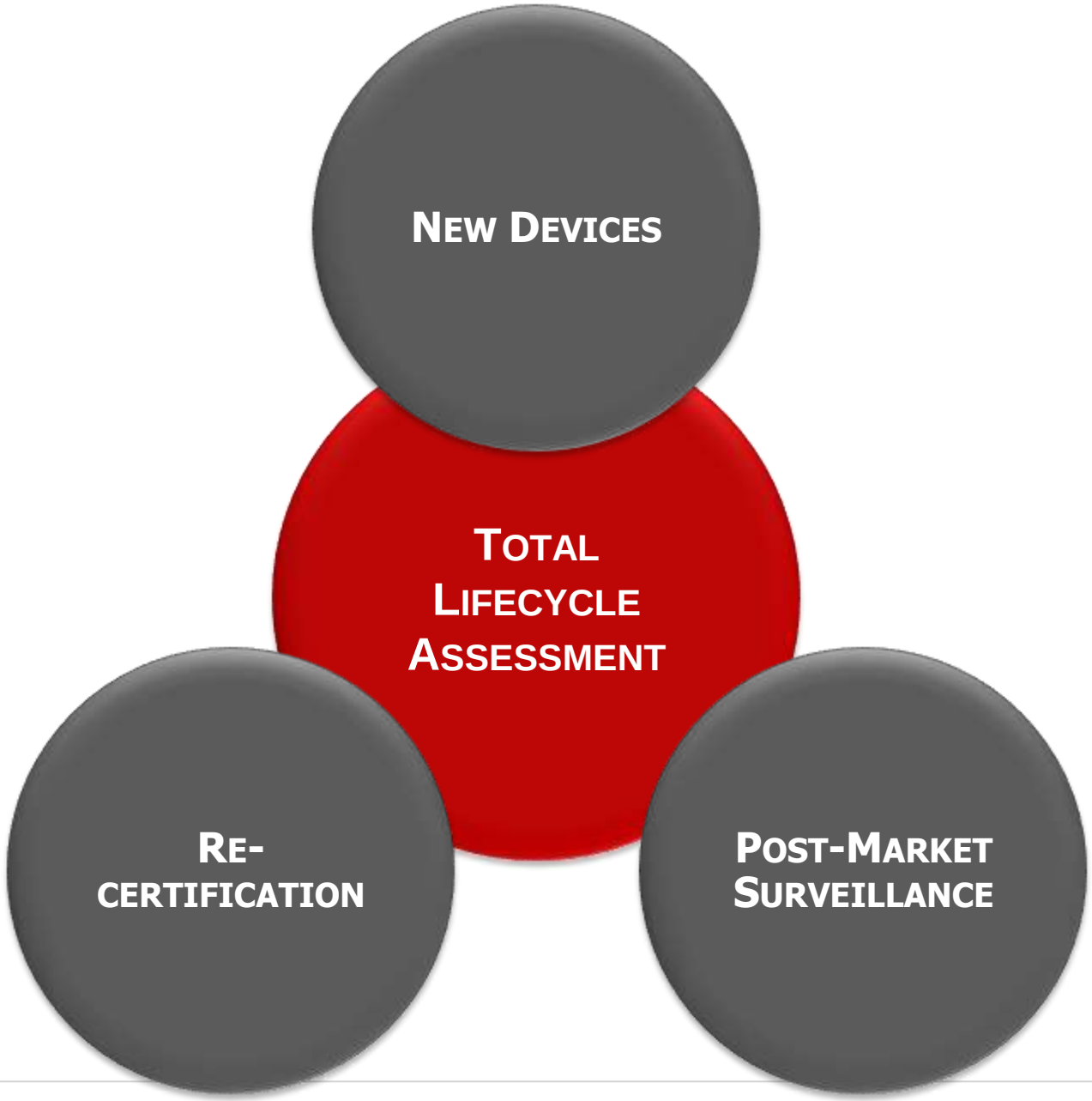
EU Regulatory Evaluation of Drugs vs. Devices

Table 2 Comparison of the regulatory evaluation of pharmaceutical products and high-risk medical devices in the EU

	Pharmaceutical products	Medical devices
Organization responsible for granting market access	• European Medicines Agency (about 90%) • National authorities (≍10%)	• Notified bodies
Types of organizations that bring products to market	• Mostly large and established pharmaceutical companies	• Variable: many start-ups and small and medium enterprises, as well as large medical technology companies
Time when clinical evidence is generated	• Generally pre-market	• Both pre- and post-market studies
Clinical development phases	• Highly standardized (Phases 1–4)	• Less standardized • Product dependent
Clinical study design	• Highly standardized • Double-blind randomized controlled trial expected	• Less standardized • Pivotal trials often done after CE marking
Irreversible effects on study subjects	• Rare	• Common, particularly with permanent implants

Reprinted with permission from Fraser *et al.*[54]

Windecker S, Gilard M et al. European Heart Journal 2024


New Devices
Total Lifecycle Assessment
Re-certification
Post-Market Surveillance

THE NEW EUROPEAN MEDICAL DEVICE REGULATION

Chapter 1 – General Requirements

Manufacturers shall establish, implement, document and maintain a risk management system.

Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating.

In carrying out risk management manufacturers shall:

(a) establish and document a risk management plan for each device

(b) identify and analyse the known and foreseeable hazards

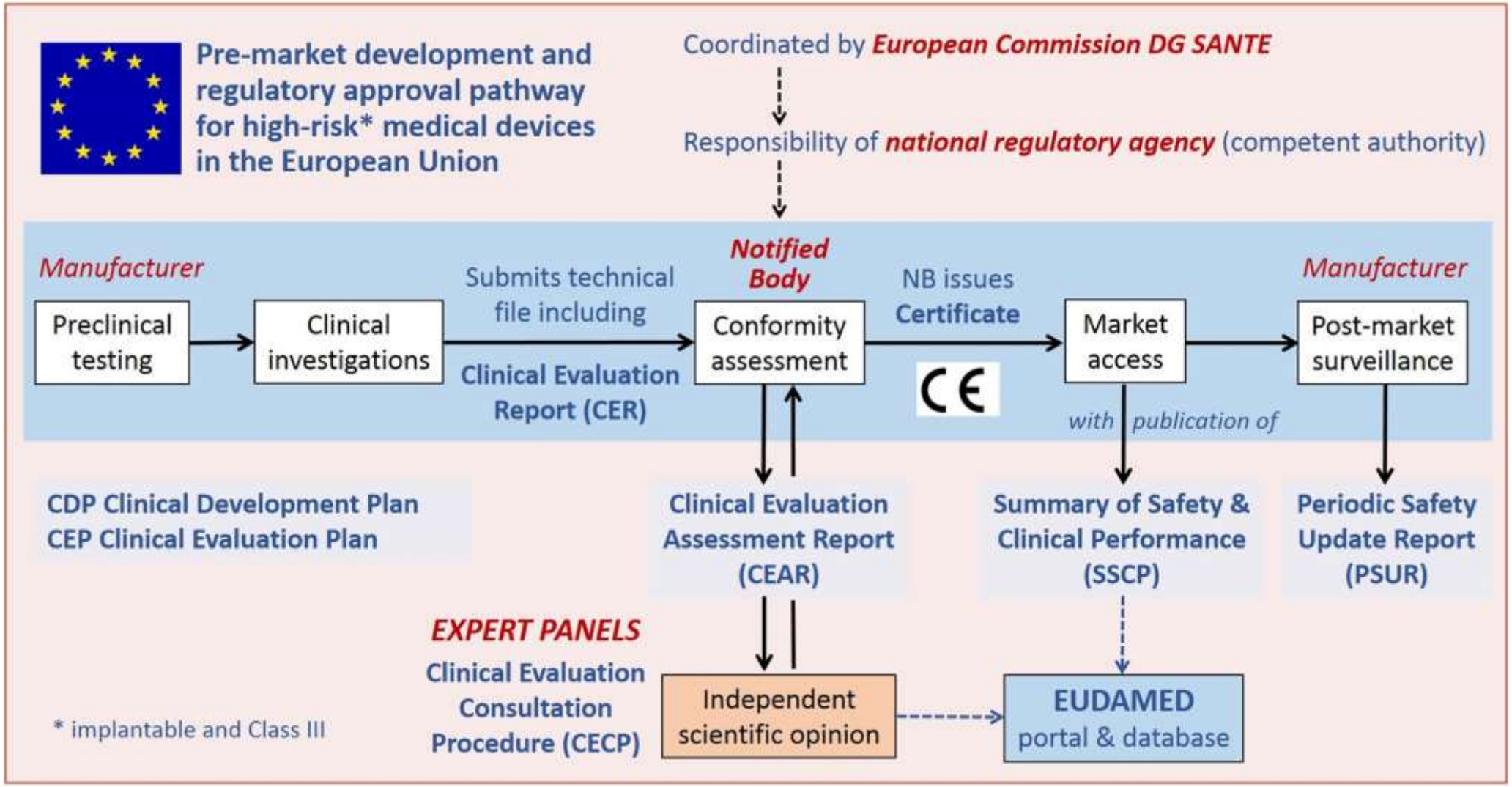
(c) estimate and evaluate the risks associated with the intended use and during reasonably foreseeable misuse

(d) eliminate or control the risks referred to in point (c)

(e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability

(f) if necessary amend control measures

The New European Medical Device Regulation (MDR)

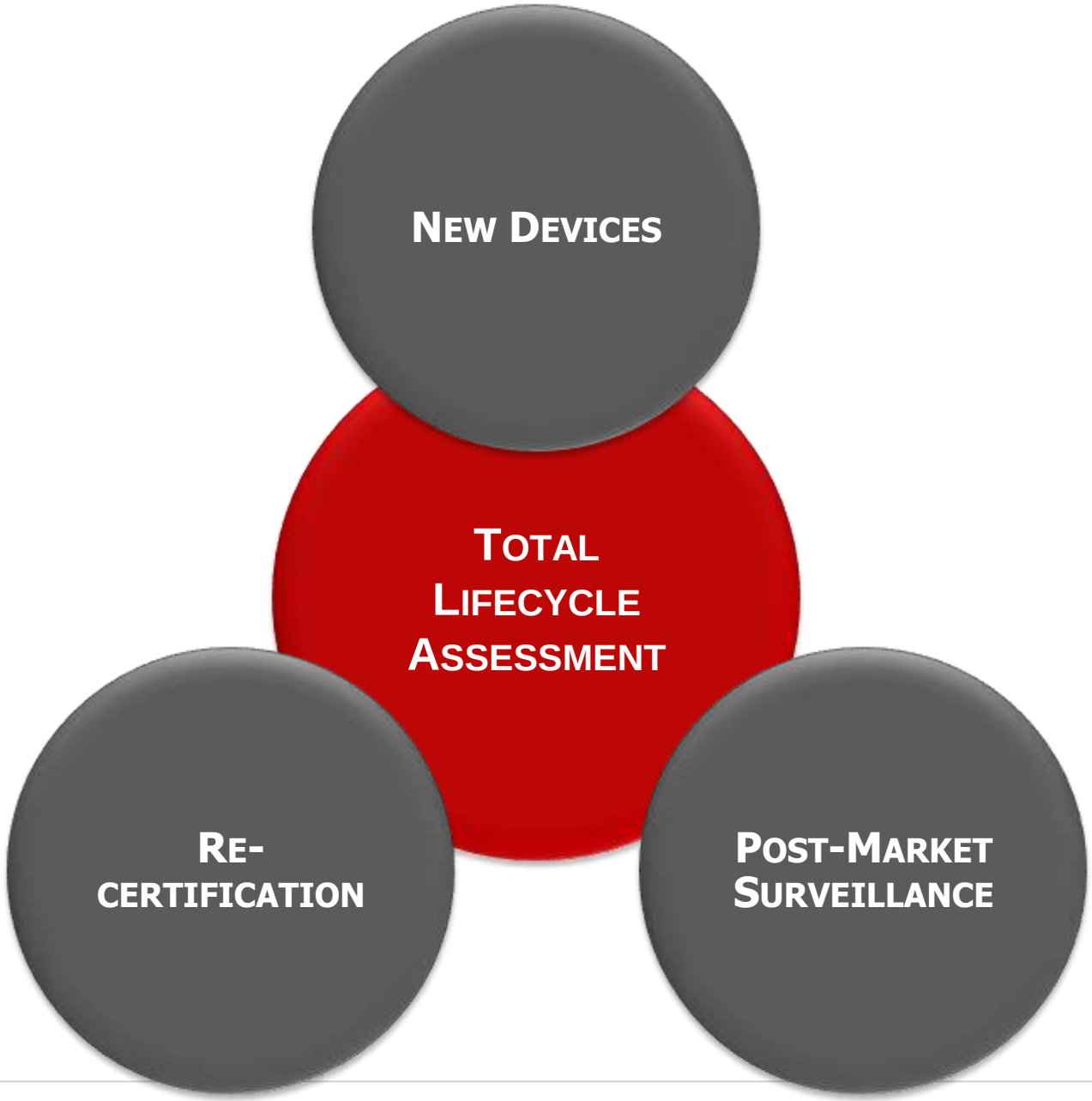


Fraser A et al. *European Heart Journal* 2020

Key Elements of MDR Changes

- Clearer criteria for high-risk devices—clinical data requirements, safety/performance criteria, common specifications, and 'scrutiny' procedure
- Robust governance, coordination, and cooperation
- Increased communication, data transparency, and device traceability
- Better performing notified bodies—enhanced requirements for notified bodies and their oversight by authorities
- Enhanced market surveillance—defined requirements, improved systems, and obligations for manufacturers and authorities

Windecker S, Gilard M et al. European Heart Journal 2024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POST-MARKET SURVEILLANCE IN EU

'Post-market surveillance'
systematic procedure to collect data proactively and review experience gained from devices placed on the market

''Post-market clinical follow-up' (PMCF)
the continuous process that updates the clinical evaluation by analyzing new clinical data to verify the safety and performance of a device.

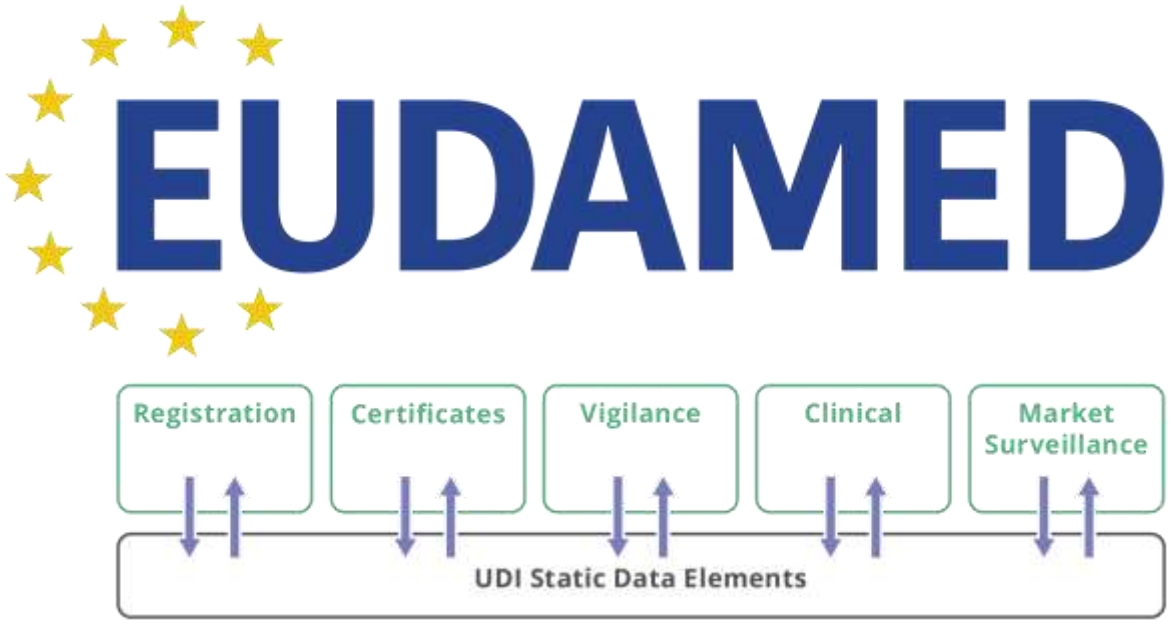
Periodic safety update reports (PSUR)
For all Class IIb and III devices at least annually

- Submitted to notified body
- Available to national competent authorities **(through EUDAMED)**
- Included in the Summary of Safety and Clinical Performance (SSCP)

Fraser A et al. *European Heart Journal* 2020

Post-Market Surveillance in EU: the European Database on Medical Devices

EUDAMED is a collaborative system that integrates different electronic systems to collate and process information about medical devices and manufacturers



- In the EU, manufacturers are obliged to plan for **passive and active surveillance**.
- EU Member states have individual requirements for reporting adverse events
- Results of surveillance are used to update the Clinical Evaluation Report and must be submitted to the European Databank on Medical Devices to which manufacturers submit a **Summary of Safety and Clinical Performance** (SSCP).

Data to be publicly available in the Summary of Safety and Clinical Performance (SSCP) on the Eudamed database

Device identification and general information
•Device trade name(s), manufacturer
•Basic unique device identification code (UDI-DI)
•Nomenclature of the medical device, and its risk class
•Name of the notified body that issued the certificate for the device
Intended use of the device
•Intended purpose
•Indications and target populations
•Contraindications and/or limitations
Device description
•Description of the device
•Comparison with previous generation(s) or variants of the device, if any
•Description of any accessories to be used in combination with the device

Risks and warnings
•Residual risks and undesirable effects
•Warnings and precautions
•Other relevant aspects of safety, including any field safety actions
Summary of clinical evaluation and post-market clinical follow-up
•Summary of clinical data related to equivalent device, if applicable
•Summary of clinical data from investigations of the device before the CE marking
•Summary of clinical data from other sources, if applicable
•An overall summary of the clinical performance and safety
•Ongoing or planned post-market clinical follow-up
Possible diagnostic or therapeutic alternatives
Suggested profile and training for users
Reference to any harmonized standards and common specifications applied

European Commission, Medical Device Coordination Group Document MDCG 2019-9.
Summary of safety and clinical performance. A guide for manufacturers and notified bodies. 2019

Post-Market Surveillance from US FDA Perspective

Current **passive** surveillance systems employed by the FDA include:

- ***MAUDE Database*** includes medical device reports submitted to the FDA by mandatory reporters (manufacturers, importers, device user facilities) and voluntary reporters (health care professionals, patients and consumers)

- ***National Evaluation System for health Technology (NEST):*** a collaborative database intended to link and synthesize data from different sources across the medical device landscape, including clinical registries, electronic health records, and medical billing claims.

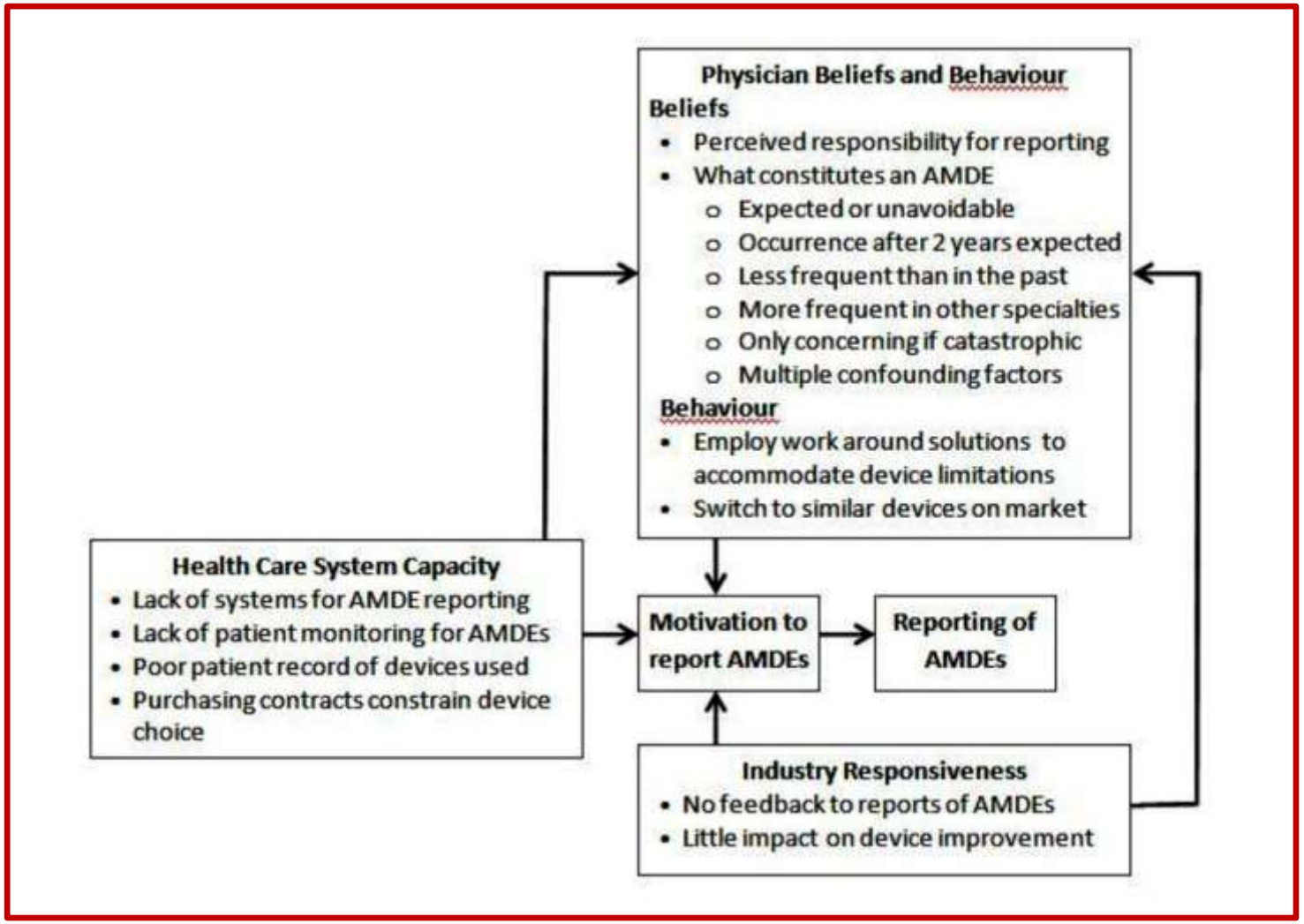
- **FDA's Sentinel Initiative** utilizes electronic healthcare data from various sources to track and analyze real-world outcomes of drugs, vaccines and devices. The goal is to detect and investigate potential safety issues more quickly and efficiently than traditional methods, ultimately enhancing patient safety.

Post-Market Surveillance from US FDA Perspective

FDA Mandatory post-market studies, commitments, requirements or reports are required of or agreed to by a sponsor that are conducted after FDA has approved a product for marketing

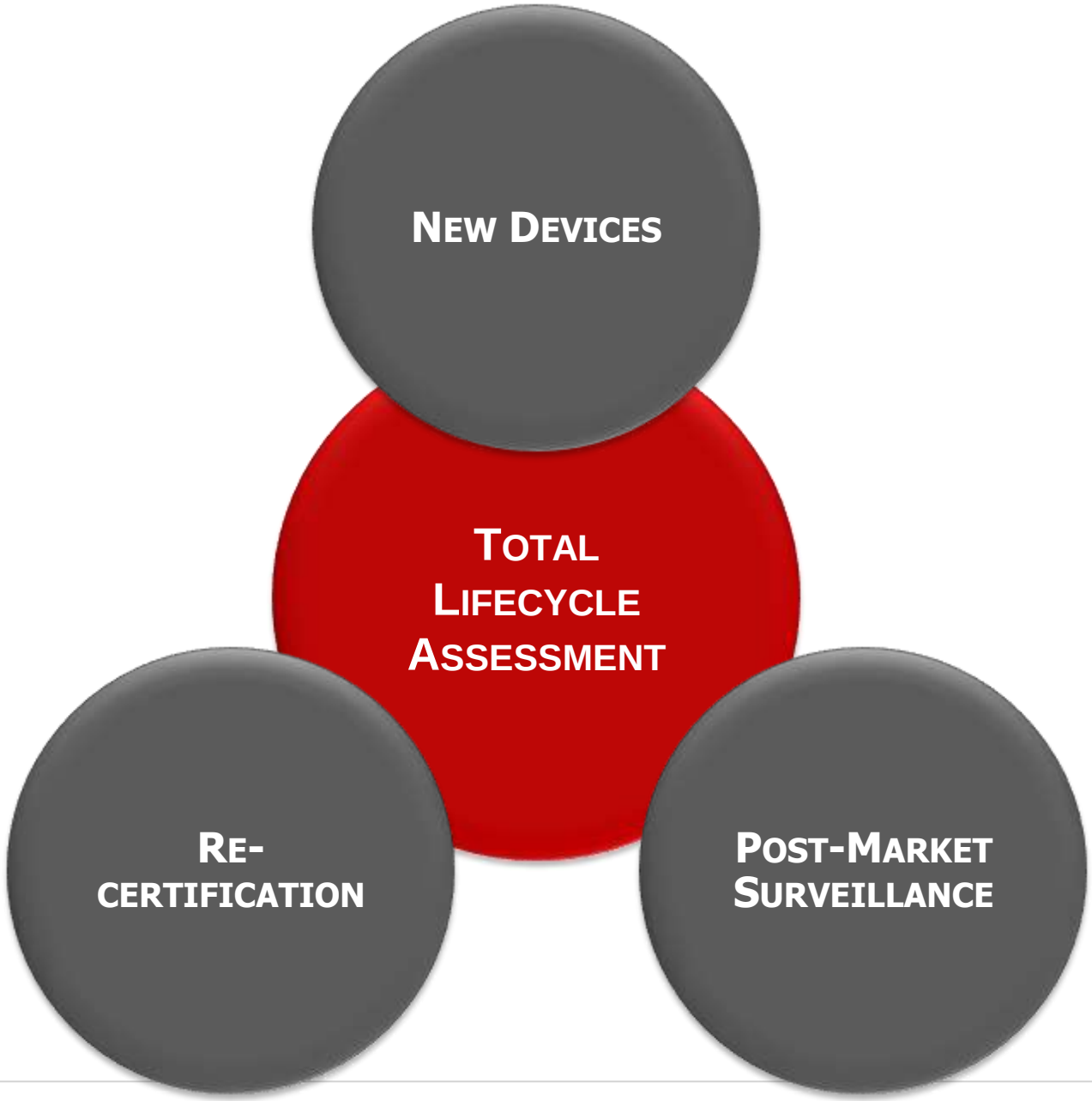
522 Studies	evaluate specific aspects of, or overall device performance once a device is available on the market; often instigated when there are concerns or uncertainties about a device
Post-Approval Studies (PAS)	gather additional data on a device's long-term safety, performance and effectiveness, and submit interim results to the FDA as studies are carried out
Recalls	report any action by manufacturers to recall, withdraw or correct a device
Annual reports	cover areas like performance and changes to labelling or manufacturing of Class III or complex devices
Periodic reports	address ad-hoc FDA requests for updated safety data, manufacturing changes, or results from ongoing clinical studies

Pitfalls in Post-Market Surveillance



- **Under-reporting of device-related adverse events is common across physicians**
- **Most common reasons include the fact that reporting events is perceived as unnecessary, impossible, or futile**

Gagliardi A et al. BMJ Qual Saf. 2018 Mar;27(3):190-198.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Re-certification in The MDR Era

The NB shall have **documented procedures for re-certification**

Re-certification **shall occur at least every 5 years**.

Require the manufacturer **to submit a summary of changes and scientific findings for the device**

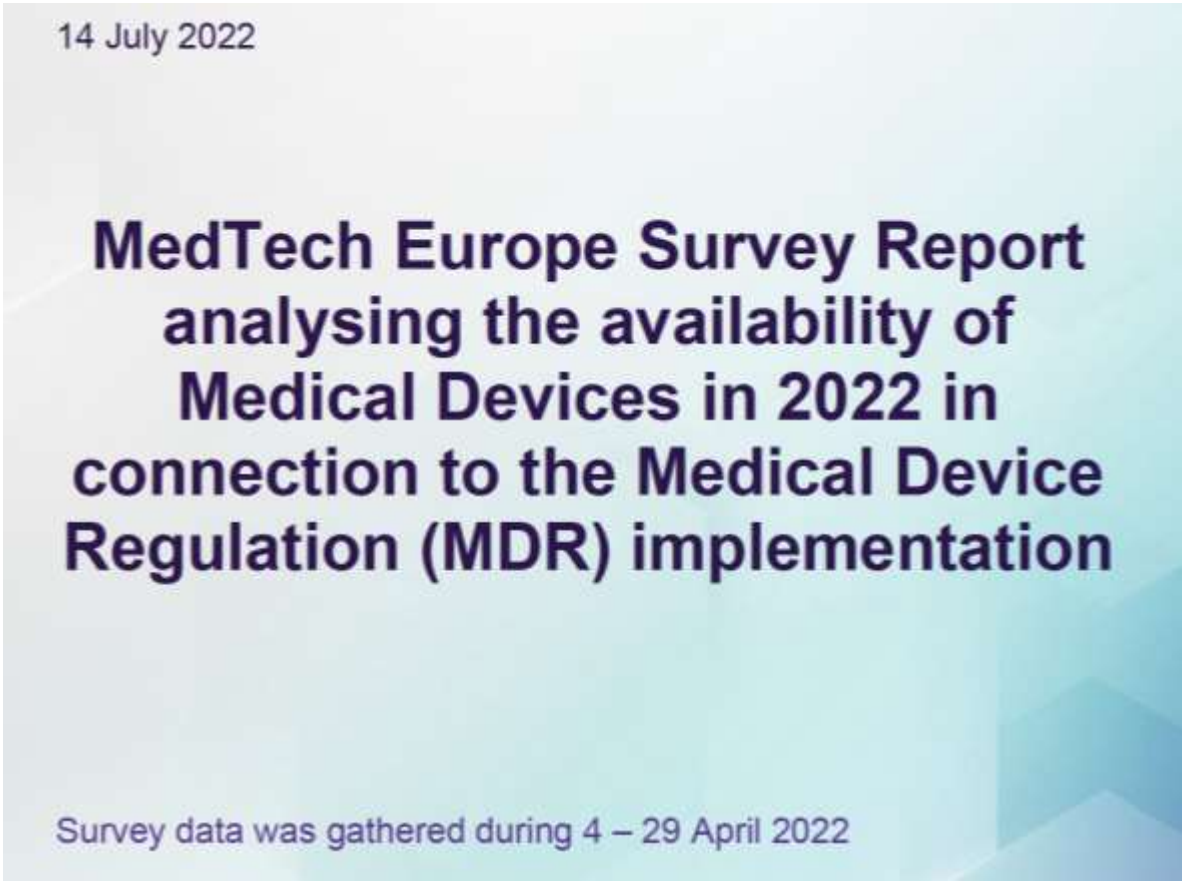
(a) all **changes** to the originally approved device, including changes not yet notified
(b) experience gained from **post-market surveillance**
(c) experience from **risk management**
(d) experience from **updating the proof of compliance** with the general safety and performance requirements
(e) experience from **reviews of the clinical evaluation**
(f) changes to **the requirements, to components of the device** or to the scientific or regulatory environment
(g) changes to applied or new harmonised standards, CS or equivalent documents
(h) changes in medical, scientific and technical knowledge

Decisions on Re-certification

For the decision on re-certification, the NB in question shall use the **same methods and principles as for the initial certification** decision.

If necessary, **separate forms shall be established** for re-certification taking into account the steps taken for certification such as application and application review.

RE-CERTIFICATION: CURRENT STATUS



- **Less than 70 000 of the almost 500 000 devices requiring recertification under MDR had been completed.**
- **The estimated time to certification was 13–18 months, which is twice as long as historically required.**
- **Most important challenges with recertification:**
  1. **lack of predictability**
  2. **lack of responsiveness,**
  3. **non-standardized interpretation** of MDR MDCG guidance by notified bodies.

KEY MESSAGES

A standardized, harmonized and robust comprehensive assessment of medical devices lifecycle assures patient safety

Initial evaluation of a new device requires to foresee a total lifecycle assessment

A rigorous and transparent post-market surveillance is pivotal

Recertification process ensures compliance with regulatory standards and potentially further improves the assurance of patient safety but the implementation is challenging

A continuous interaction between stakeholders (regulatory authorities, physicians, scientists, industry and patients) is pivotal to allow an effective and sustainable total lifecycle assessment