Disclaimer of Liability

This presentation is based on current publicly available information documented in the references at the end of this presentation and created to the best of my knowledge as a clinical subject matter expert for medical devices.

This presentation **does not reflect the views and processes of QMD Services GmbH** and only represents my personal understanding of the regulatory requirements for medical devices in the EU.

BECAUSE PATIENT SAFETY MATTERS.

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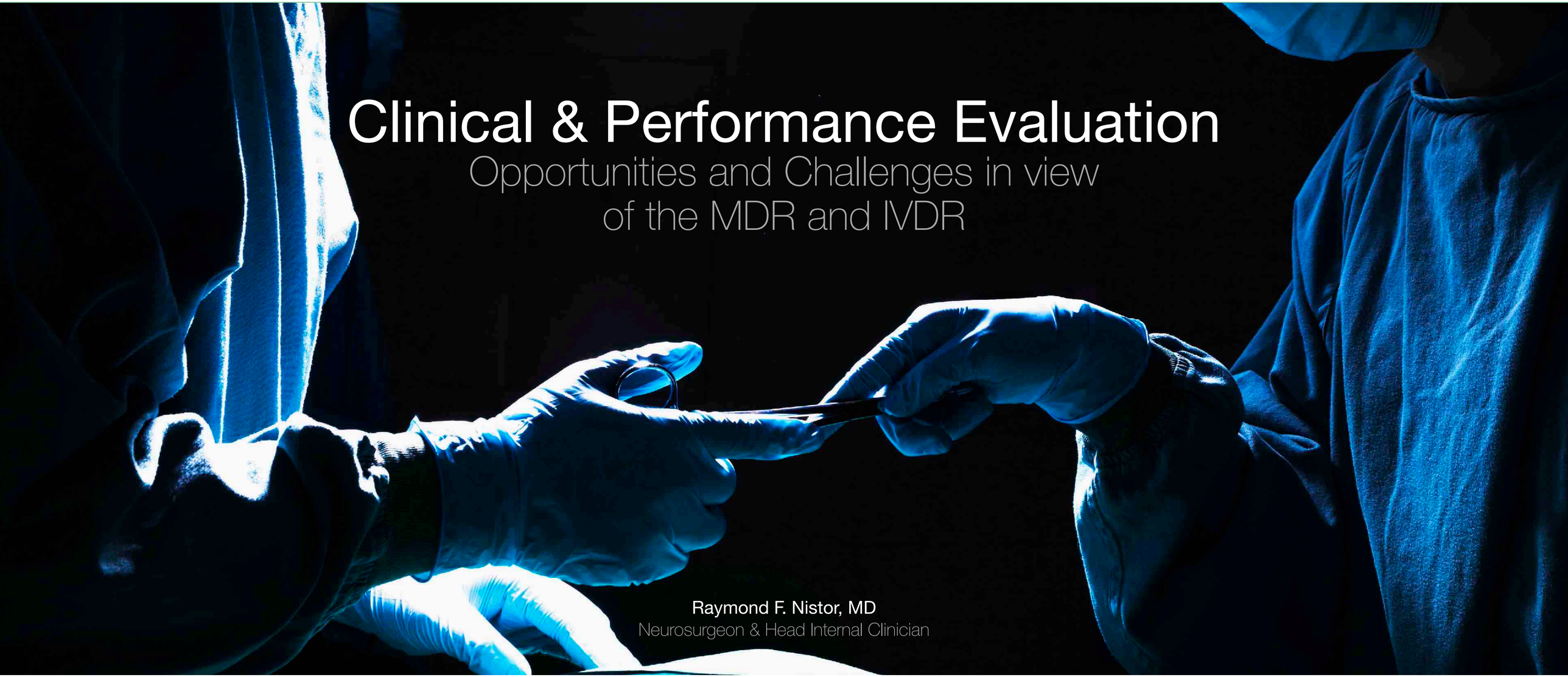


Clinical & Performance Evaluation

Opportunities and Challenges in view of the MDR and IVDR

Raymond F. Nistor, MD
Neurosurgeon & Head Internal Clinician

1

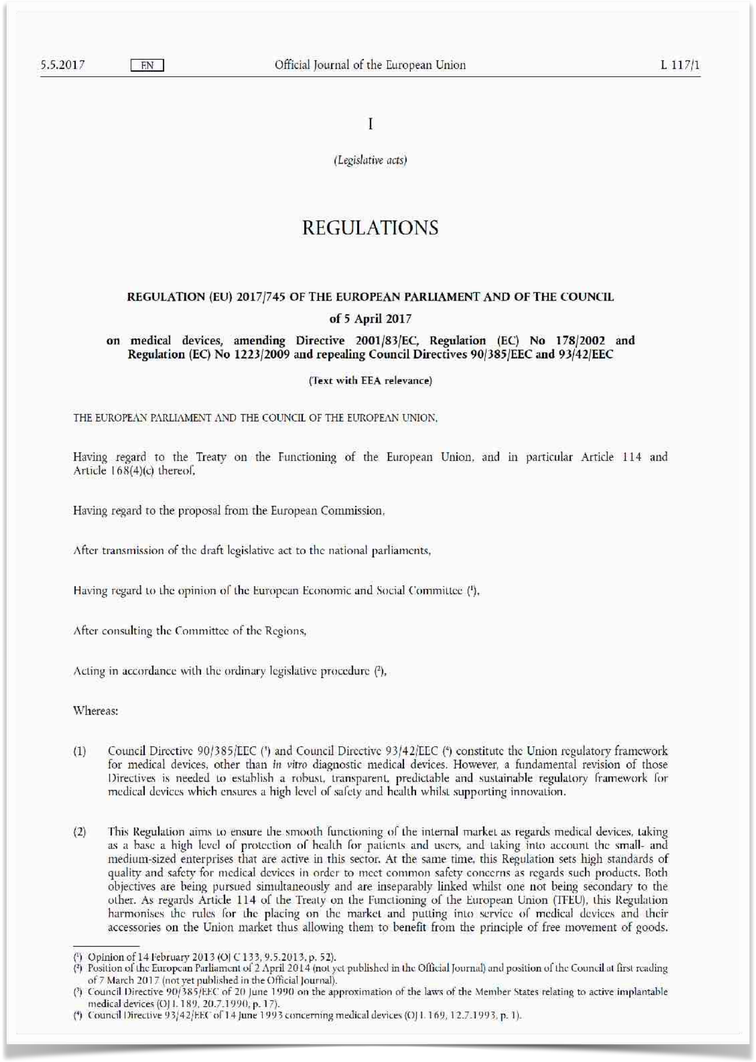
MDR & IVDR

A fundamentally new perspective and a to be welcomed intention

Source: BYRÅKRATMONSTERET (regi: Thomas Simonsen Balmbra, Norge)

The Medical Device Regulation (MDR)

Regulation (EU) 2017/745 - the key message



5.5.2017 EN Official Journal of the European Union L 117/1

I

(Legislative acts)

REGULATIONS

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee (1),

After consulting the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure (2),

Whereas:

(1) Council Directive 90/385/EEC (3) and Council Directive 93/42/EEC (4) constitute the Union regulatory framework for medical devices, other than *in vitro* diagnostic medical devices. However, a fundamental revision of those Directives is needed to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices which ensures a high level of safety and health whilst supporting innovation.

(2) This Regulation aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the small- and medium-sized enterprises that are active in this sector. At the same time, this Regulation sets high standards of quality and safety for medical devices in order to meet common safety concerns as regards such products. Both objectives are being pursued simultaneously and are inseparably linked whilst one not being secondary to the other. As regards Article 114 of the Treaty on the Functioning of the European Union (TFEU), this Regulation harmonises the rules for the placing on the market and putting into service of medical devices and their accessories on the Union market thus allowing them to benefit from the principle of free movement of goods.

(1) Opinion of 14 February 2013 (OJ C 133, 9.5.2013, p. 52).
(2) Position of the European Parliament of 2 April 2014 (not yet published in the Official Journal) and position of the Council at first reading of 7 March 2017 (not yet published in the Official Journal).
(3) Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (OJ L 189, 20.7.1990, p. 17).
(4) Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ L 169, 12.7.1993, p. 1).

Key elements of the new regulatory approach, such as the supervision of notified bodies, conformity assessment procedures, clinical investigations and **clinical evaluation**, vigilance and market surveillance **should be significantly reinforced**, whilst provisions ensuring **transparency** and traceability regarding medical devices are being introduced, **to improve health and safety**.

https://eur-lex.europa.eu/legal-content/de/ALL/?uri=CELEX:32017R0745

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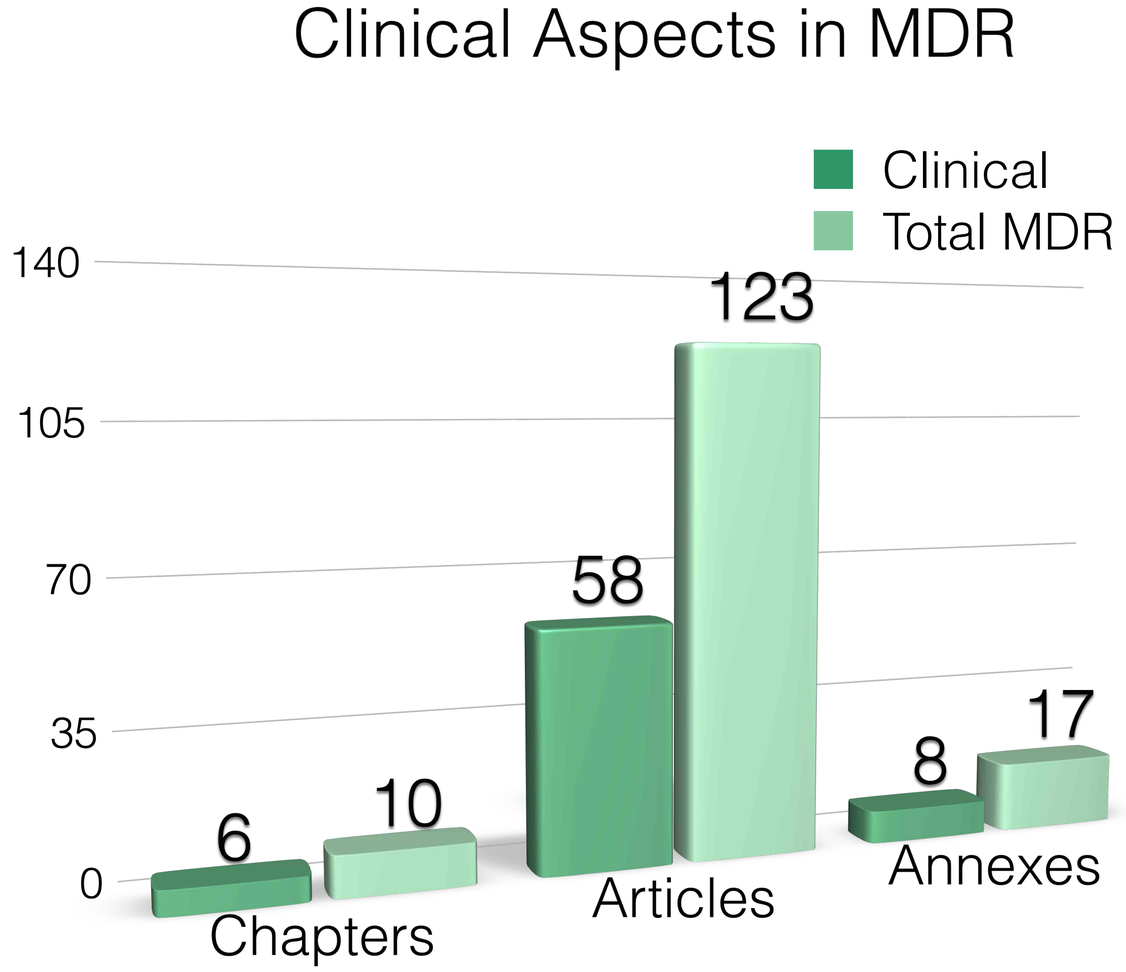
1 MDR ≈ 50% Clinical Aspects

clinical aspects are key and new



6 of 10 chapters: **III-VIII**

58 of 123 articles: **32, 35-50, 54, 55, 61-82, 83-100, 120, 123**

8 of 17 annexes: **I-III, IX, X, XIII-XV**

1 Clinical Performance
is different in MDR Vs. IVDR

Regulation (EU) 2017/745 MDR

MDR Art.2(52) 'clinical performance' means **the ability of a device**, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, **to achieve its intended purpose** as claimed by the manufacturer, **thereby leading to a clinical benefit for patients, when used as intended** by the manufacturer

Regulation (EU) 2017/746 IVDR

IVDR Art.2(41) 'clinical performance' means the **ability of a device to yield results** that are **correlated with a particular clinical condition or a physiological or pathological process or state** in accordance with the target population and intended user

1 Clinical Benefit

is fundamentally different and a completely new terminology in MDR Vs. IVDR

Regulation (EU) 2017/745 MDR

MDR Art.2(53) 'clinical benefit' means **the positive impact of a device on** the **health** of an individual, **expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s)**, including outcome(s) related to diagnosis, **or a positive impact on patient management or public health**

Regulation (EU) 2017/746 IVDR

IVDR Art.2(37) 'clinical benefit' means the **positive impact** of a device related to its function, such as that **of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health**

1 The Benefit-Risk Determination

a completely new terminology used in the MDR and IVDR

Regulation (EU) 2017/745 MDR **Regulation (EU) 2017/746 IVDR**

MDR Art.2(24) and IVDR Art.2(17) 'benefit-risk determination' means **the analysis of all assessments of benefit and risk** of possible relevance **for the use** of the device for the intended purpose, when used **in accordance with the intended purpose** given by the manufacturer

IVD Clinical Benefit is Different

Specified in Legislative Act 64 (preamble) of IVDR

IS	IS NOT
accurate medical information	final clinical outcome

"the concept of clinical benefit for in vitro diagnostic medical devices is fundamentally different from that which applies in the case of pharmaceuticals or of therapeutic medical devices, since **the benefit of in vitro diagnostic medical devices lies in providing accurate medical information on patients**, where appropriate, assessed against medical information obtained through the use of other diagnostic options and technologies, whereas the final clinical outcome for the patient is dependent on further diagnostic and/or therapeutic options which could be available"[1]

1. MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software, March 2020

IVD Clinical Benefit

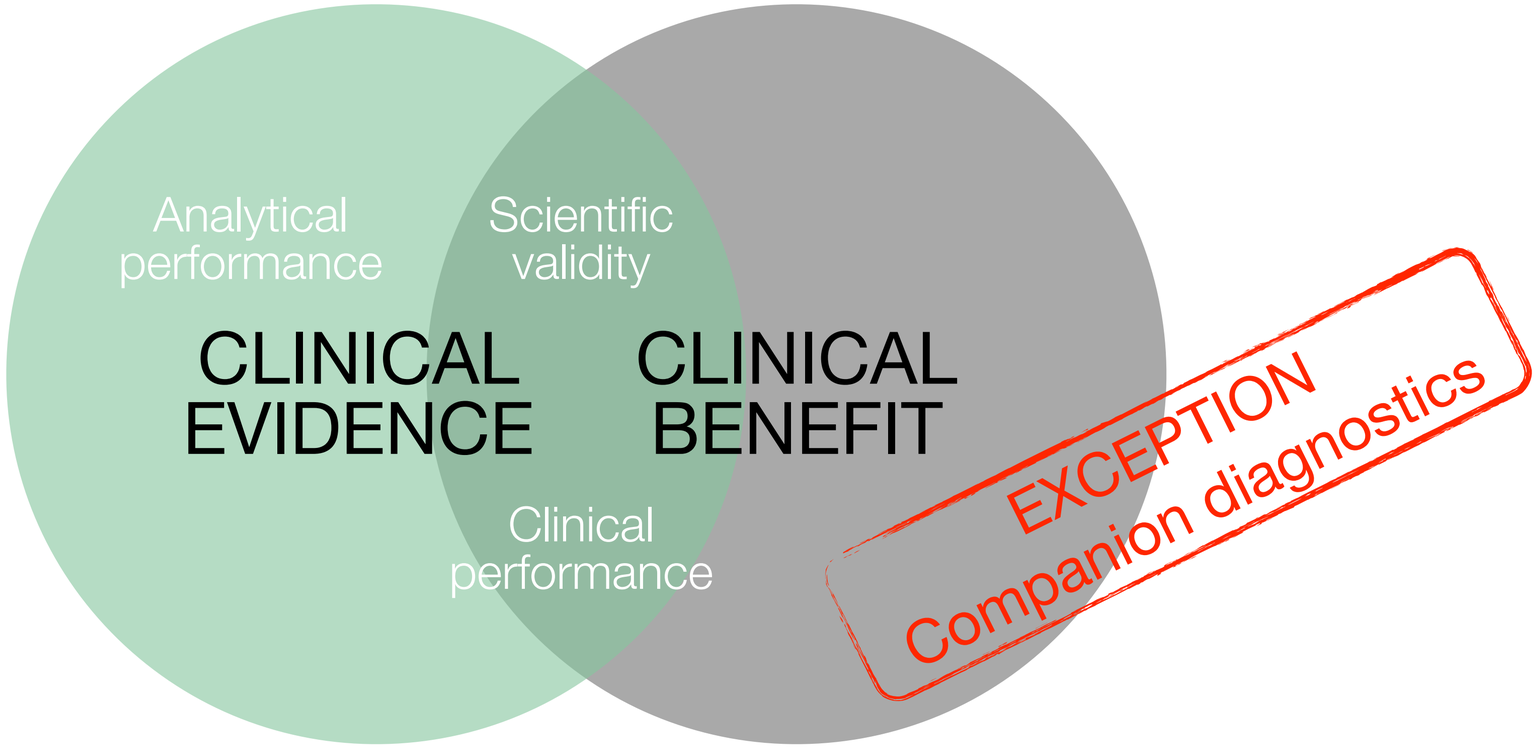
a final word

IS

accurate medical information

IS NOT

final clinical outcome



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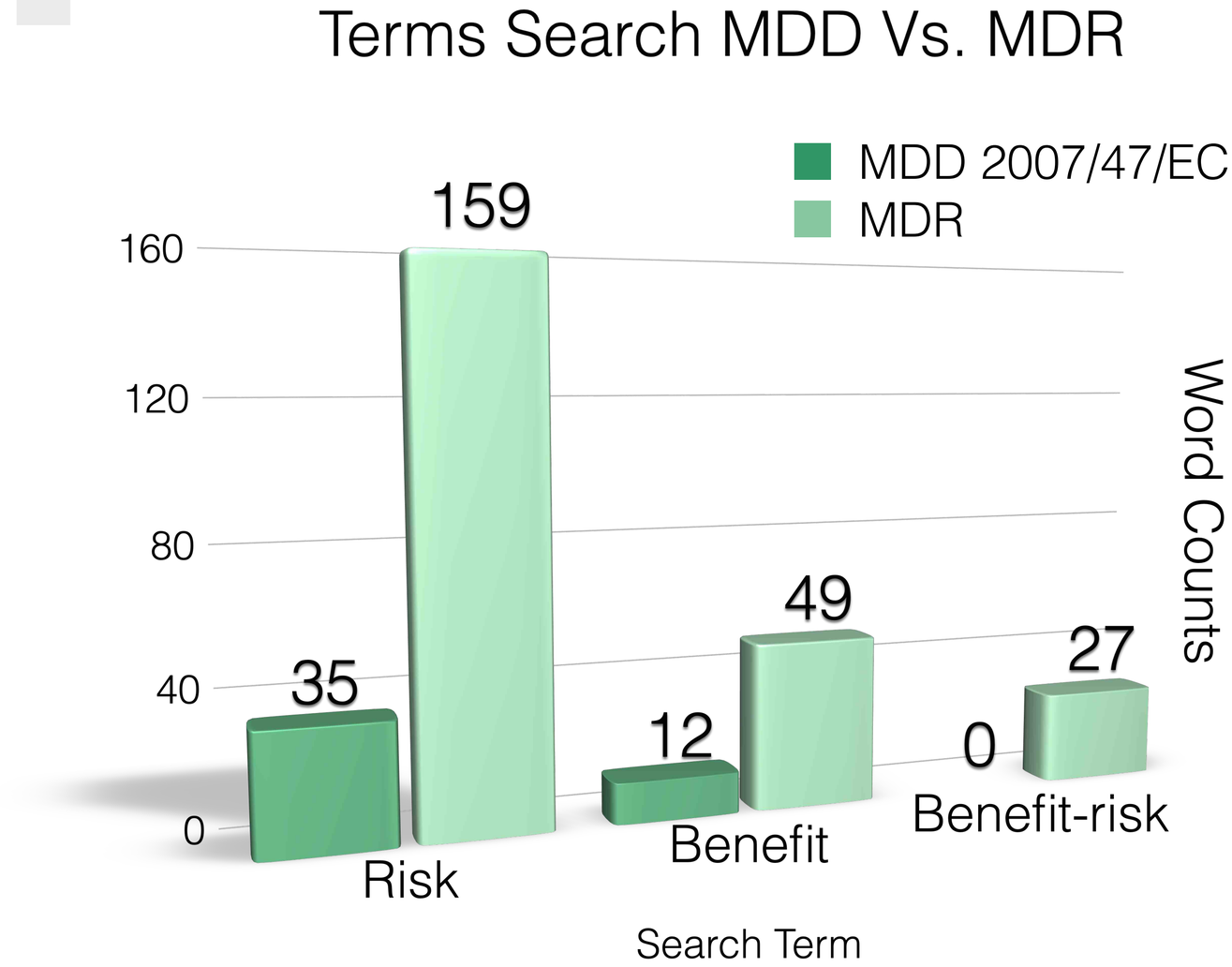
What is the Essence of MDR?

nothing but good risk management



"The **risk management system should be carefully aligned with and reflected in the clinical evaluation** for the device, including the clinical risks to be addressed as part of clinical investigations, clinical evaluation and post-market clinical follow up. **The risk management and clinical evaluation processes should be interdependent and should be regularly updated.**"

Legislative Act 33 for MDR

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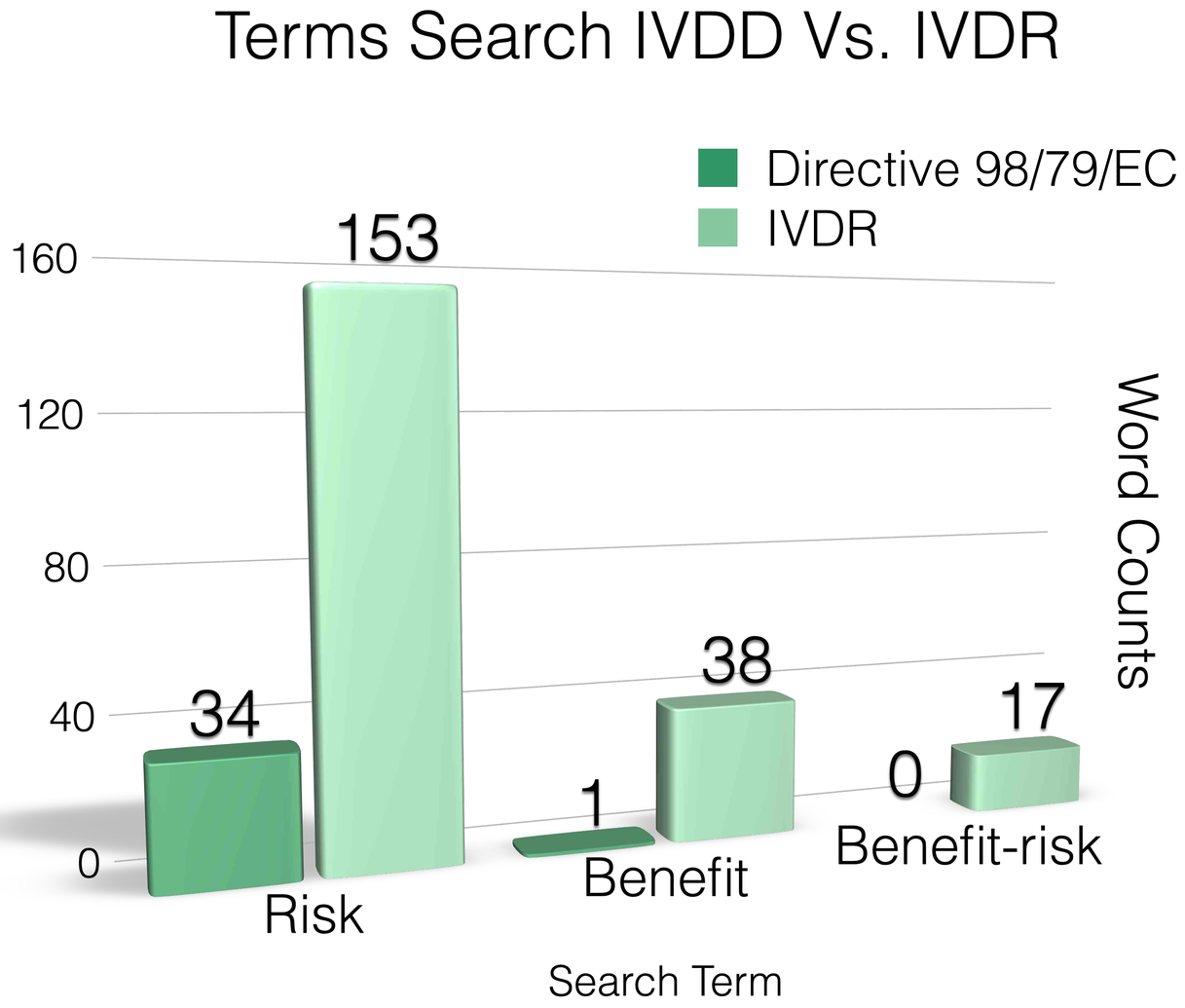
What is the Essence of IVDR?

nothing but good risk management



”The **risk management system should be carefully aligned with and reflected in the performance evaluation process** for the device, including the clinical risks to be addressed as part of performance studies, performance evaluation and post-market performance follow-up. **The risk management and performance evaluation processes should be inter-dependent and should be regularly updated**”

Legislative Act 32 of IVDR

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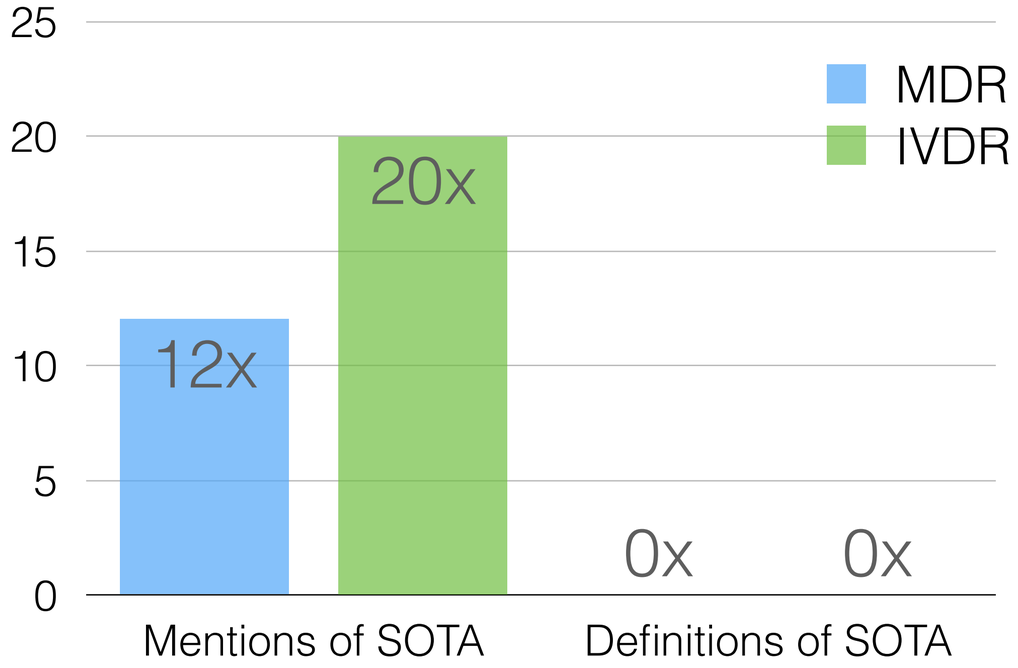
State of the Art (SOTA)

ISO 14971 has the answer



State of the art (3.28) "Developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience."

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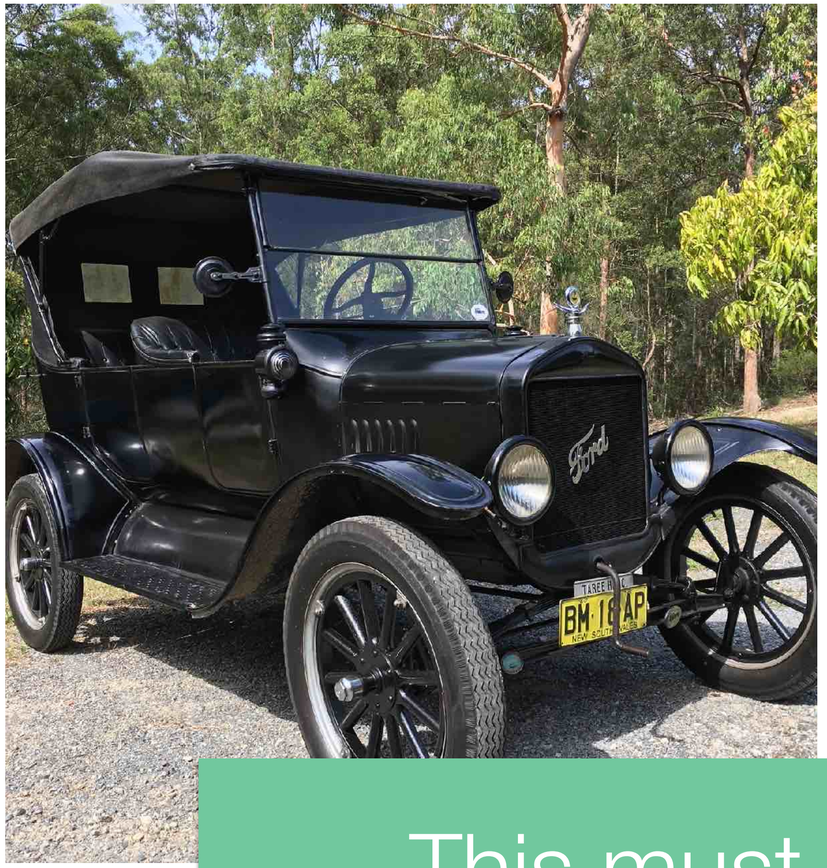
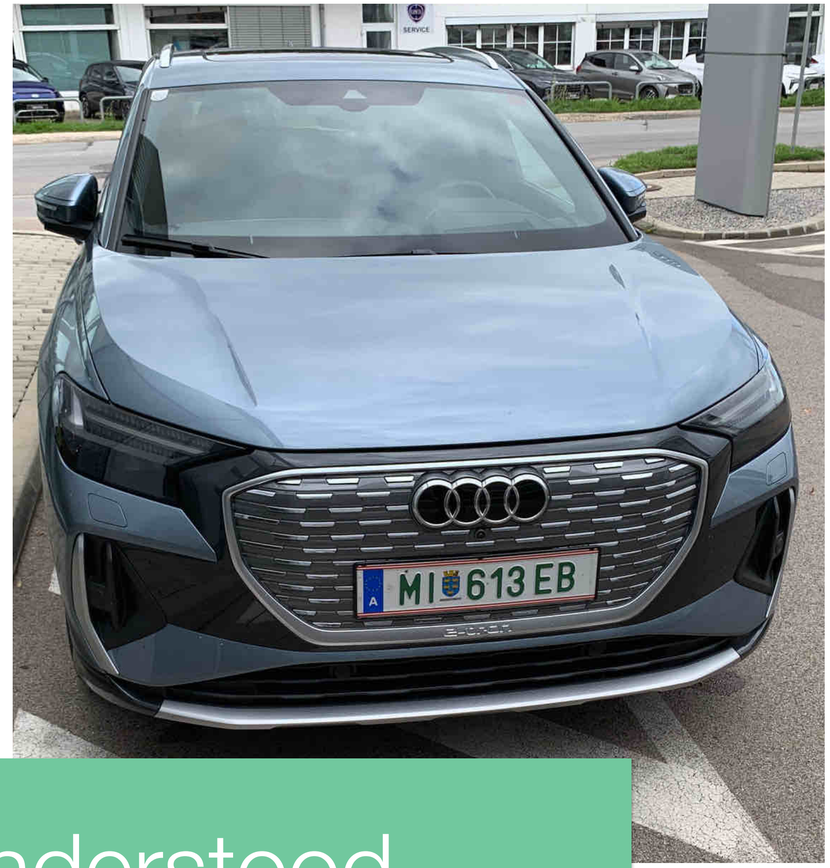
What is State of the Art

nothing but confusion





This must be unambiguously understood.

4

State of the Art & Clinical Benefit

are interrelated and simple to explain for therapeutic devices

Figure A.5.1
Adjusted patient survival by modality: Incident dialysis patients
from day 91, adjusted for age, sex, and primary renal disease

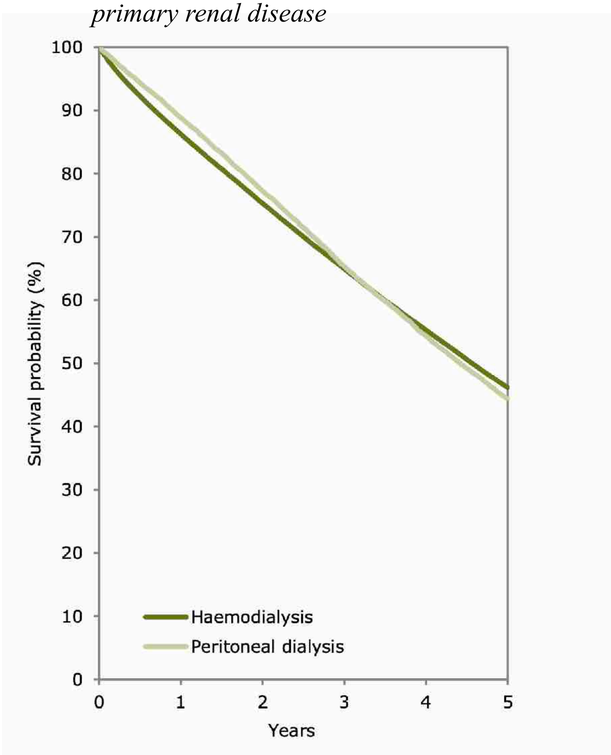


Figure A.5.2
Adjusted patient survival by donot type: Patients receiving a first kidney transplant
from day of transplant, adjusted for age, sex, and primary renal disease

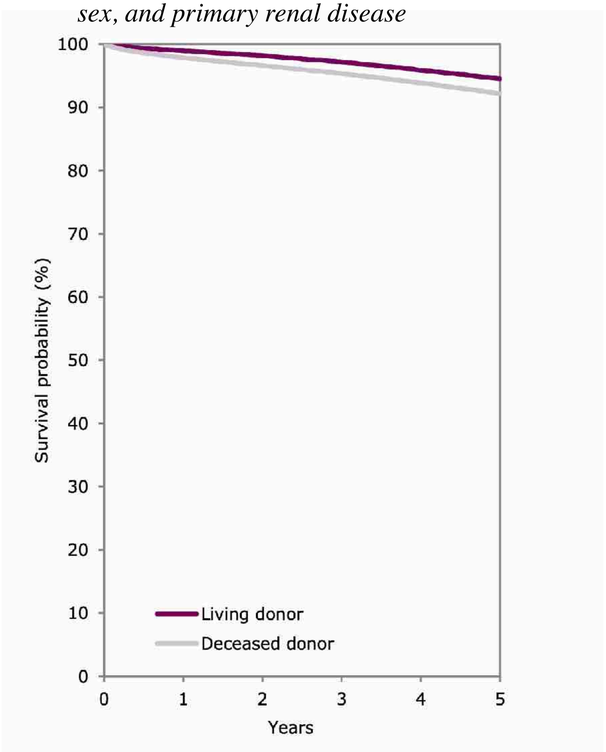
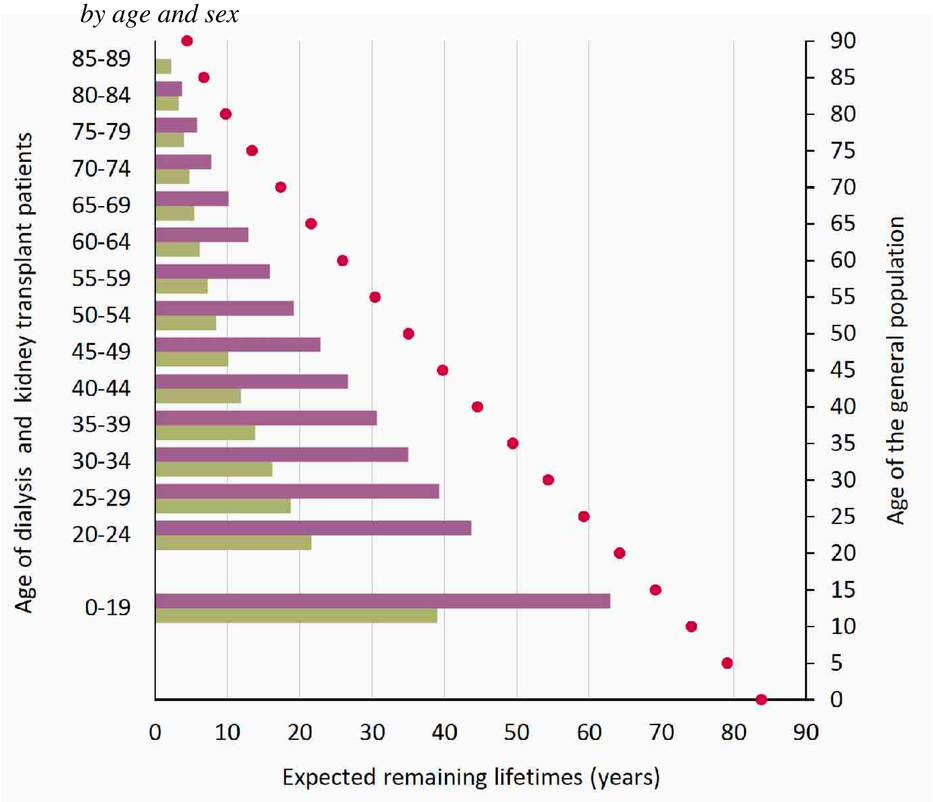


Figure A.6.1
Expected remaining lifetimes (years) of the general population (cohort 2013-2017) and of prevalent dialysis and kidney transplant patients (cohort 2013-2017)
by age and sex



Sourced from: European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry - Annual Report 2017; ISBN 978-90-830309-0-6

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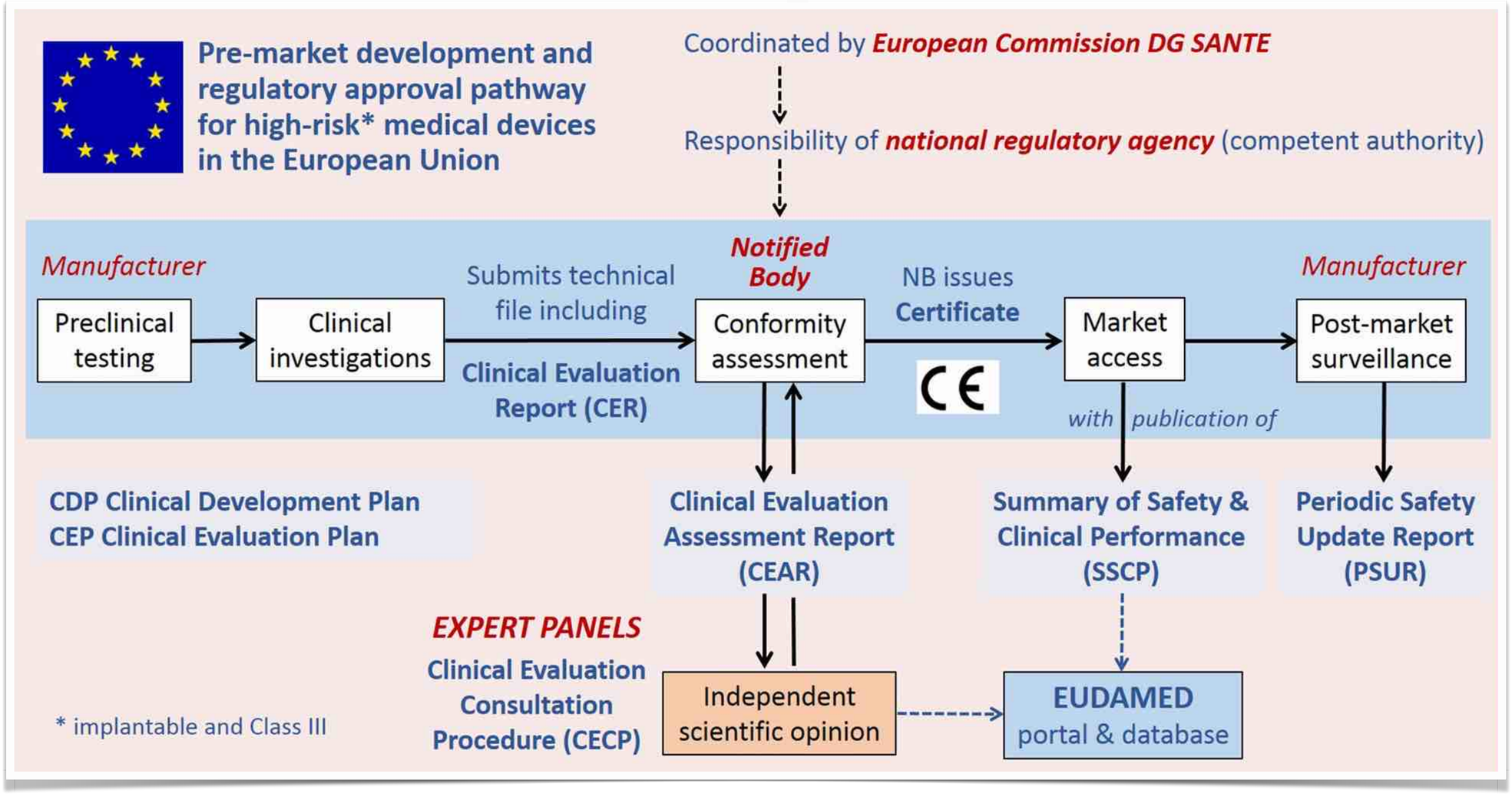

Fraser AG, et al. Implementing the new European Regulations on medical devices—clinical responsibilities for evidence-based practice: a report from the Regulatory Affairs Committee of the European Society of Cardiology, *European Heart Journal*, Volume 41, Issue 27, 14 July 2020, Pages 2589–2596, https://doi.org/10.1093/eurheartj/ehaa382

2

MAJOR NON-CONFORMITIES

The most common issues seen in respect to CER/PER

2 Clinical Evaluation

should be the output of the device risk management review

"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"

Device Clinical Data	Indirect Clinical Data	Relevant Literature	Post Market Data
1	2	3	4

* CER = Clinical Evaluation Report

2 Clinical Investigations

MEDDEV 2.7/1 rev 4 §9.3.1 und MDR Art. 61-80, 82, Ann. XV

Class III and implantable medical devices must have direct clinical data (with a few exceptions) that come from clinical trials with the medical device to be assessed

MDR Art. 61(10):

- allows the use of non-clinical data to demonstrate compliance with GSPRs[1]
- Not applicable to class III or implantable medical devices.
- May be applied to all other classes (IIa and IIb) - e.g. WET (Well Established Technologies)

MDCG 2020-6, Section 4.

Exemptions from clinical investigations require that the **clinical evaluation is based on "sufficient clinical data"**

* GSPR = General Safety and Performance Requirements = Grundlegende Sicherheits- und Leistungsanforderungen

2 Clinical Evidence
as defined in the MDR

"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."[1]

MDR (EU) 2017:745-1; Art. 2(51)

[1] REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices.

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2 Major Non-Conformities CER

Common pitfalls of CERs provided by manufacturers

A Confusion: Intended Purpose Vs. Indication for Use

B Non-equivalent equivalence

C Inappropriate analysis of AE/SAEs

D Missing literature appraisal

E Lack of analysis & evaluation of clinical data

F No clinical input into risk management

G Inappropriate clinical evaluator

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2 A. Intended Purpose Vs. Indication for Use

the difference that MDR does not explain

It is not

- the Intended Purpose or Intended Use IS NOT the Indication for Use

Is

- the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation."[1]

Mastering this common confusion helps to create a meaningful CER

[1] REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices.

2 A. Intended Purpose Vs. Indication for Use

IMDRF gives the clarification

Intended Purpose/Intended Use

“The objective intent regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.”[1] (*IMDRF GRRP WG (PD1)/N52:2018 3.16*)

Indication for Use

“A general description of the disease or condition the medical device or IVD medical device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the medical device or IVD medical device is intended.”[1] (*IMDRF GRRP WG (PD1)/N52:2018 3.14*)

Mastering this common confusion helps to create a meaningful CER

[1] IMDRF GRRP WG (PD1)/N52:2018 - Principles of Labeling for Medical Devices and IVD Medical Devices from 12 July 2018.

2 Floseal Hemostatic Matrix

An example for surgical hemostatic use

Indications

FLOSEAL is indicated in surgical procedures as an adjunct to hemostasis when control of bleeding, ranging from oozing to spurting, by ligature or conventional procedures is ineffective or impractical.

[1] Instructions for Use FLOSEAL Hemostatic Matrix 5 mL/10 mL Document No. 0735017; P2 16-FEB-2017 KLS English EU Version

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2 Floseal Hemostatic Matrix

An example for surgical hemostatic use

Intended Purpose/Intended Use

Indications

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An example for surgical hemostatic use

Indication for Use

Indications

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[1] Instructions for Use FLOSEAL Hemostatic Matrix 5 mL/10 mL Document No. 0735017; P2 16-FEB-2017 KLS English EU Version

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2 Understanding the difference
between Intended Purpose and Indication for Use

Indication for Use

When to use it?
Under which clinical circumstances?
Which pathology?
In which population?

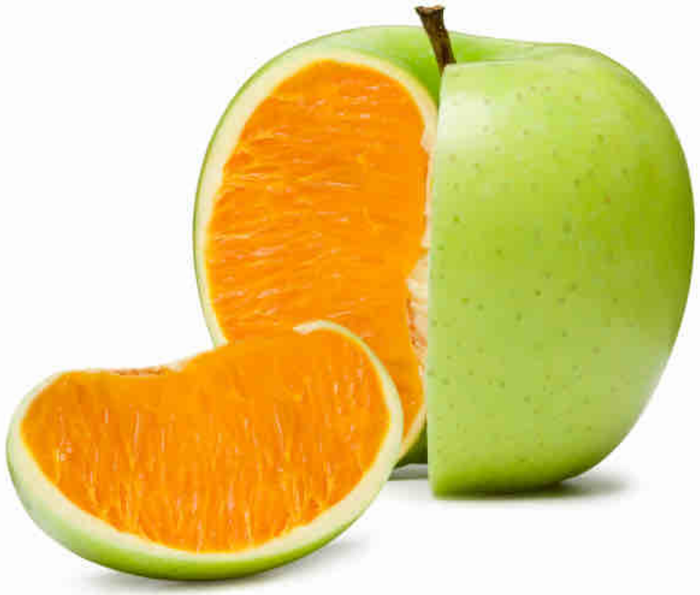
Intended Purpose/Intended Use

What does the device do in the body?
(e.g., replacement of a body part,
ablation,
hemostasis, etc.)

2 B. Non-equivalent Equivalence

Poor equivalent device choice and inadequate comparison

This is… orapple

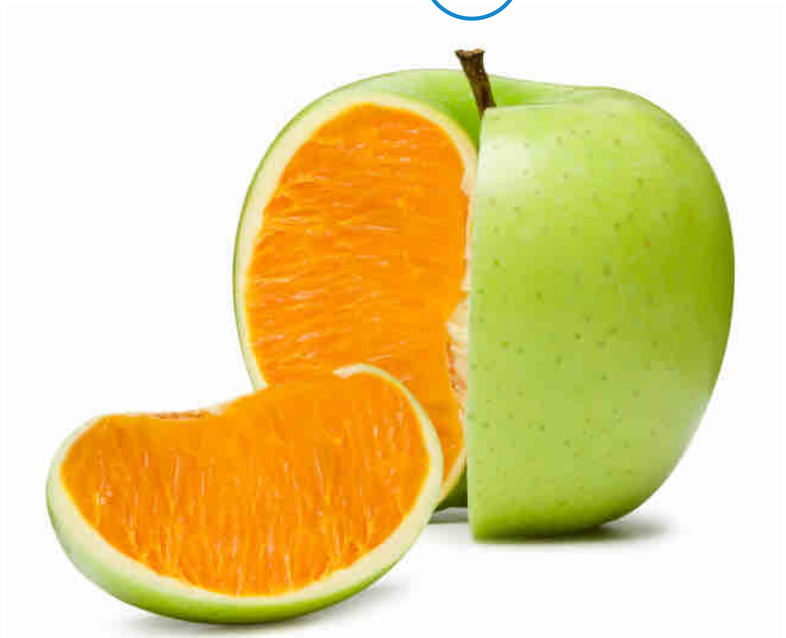


2 B. Non-equivalent Equivalence

acc. to ANNEX XIV §3: Clinical Evaluation

TECHNICAL

1



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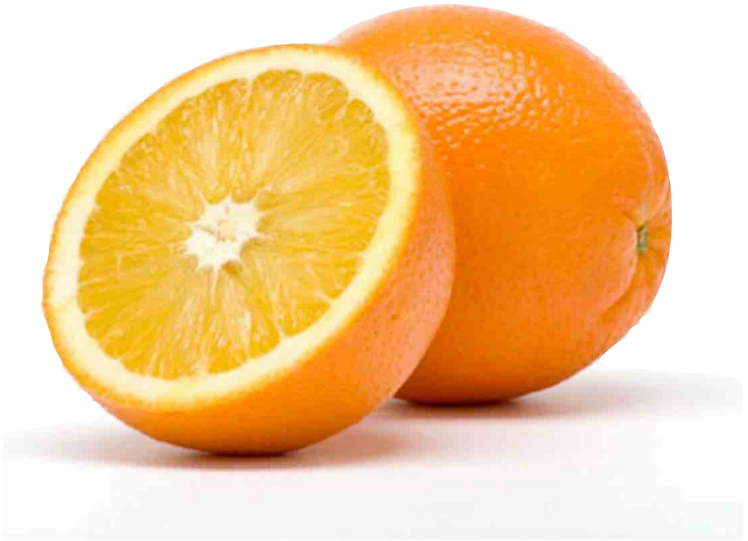
BIOLOGICAL

2



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CLINICAL

3

2 Non-equivalent Equivalence

acc. to ANNEX XIV §3: Clinical Evaluation

TECHNICAL

1

similar design
similar conditions of use
similar specifications/properties
similar handling/application
similar principles of operation
similar critical performance requirements

BIOLOGICAL

2

same materials/substances
in contact with same tissues
similar kind/duration of contact
similar release characteristics

CLINICAL

3

same intended purpose
same clinical indication
similar patient population
similar relevant critical performance

All parameters shall be **similar** to the extent that there would be **no clinically significant difference** in the safety and clinical performance of the device

Based on **proper scientific justification**

With sufficient access to equivalent device data

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2 C. Inappropriate Analysis of AE/SAEs

Not assessing critically the incidents and serious incidents

Device safety synopsis for CERs

Evaluation period (updated):

- Units shipped/sold (globally not only EU)
- Product incidents (global data)
- Product serious incidents with causal association

Historical evaluation of serious incidents:

- Units shipped/sold (globally not only EU)
- Product serious incidents (global data) with causal association
- Critical presentation of individual cases of death and permanent injury deemed related

Incidents (malfunctions and use errors) with potential safety impact:

- Malfunctions likely to cause death or serious injury
- Compare SAEs/malfunctions/use errors with harms/hazardous situations in device risk file
- Are all potential harms identified in the device labeling

2 The Major Safety Philosophy
that should drive the device safety analysis in a CER

Absence of evidence is not evidence of absence.

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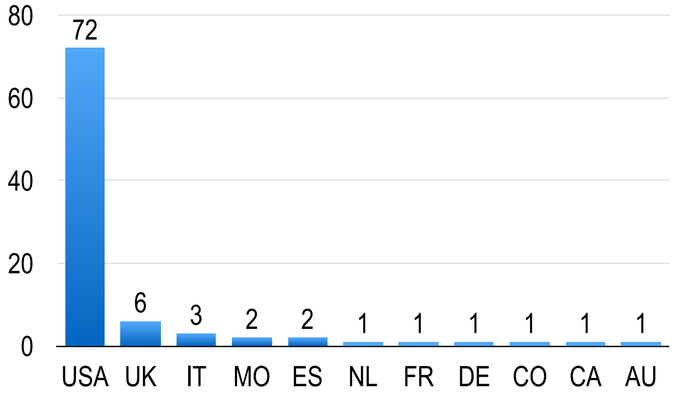
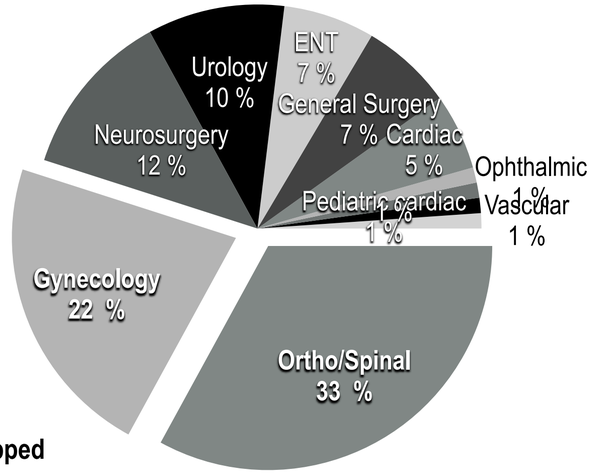
2 Safety Signal Detection

Increase in use errors in a surgical hemostat (Class III Implantable)

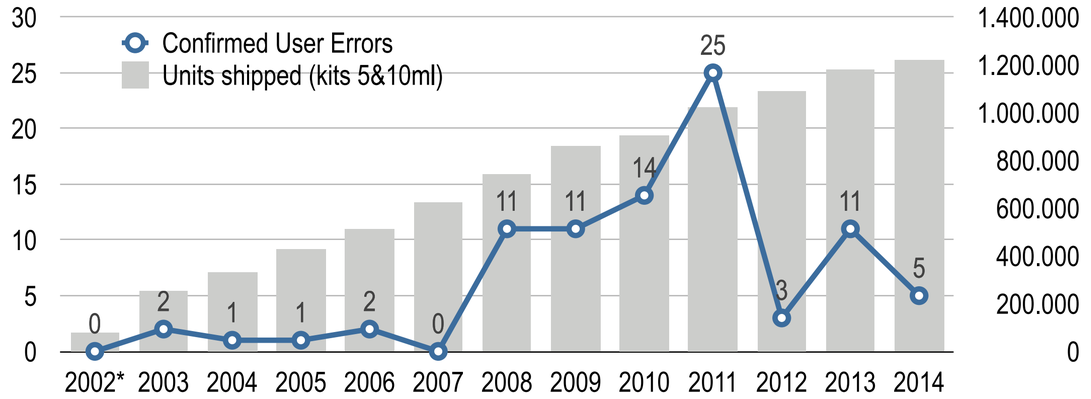
Confirmed Use Errors by Country (2002-2014)



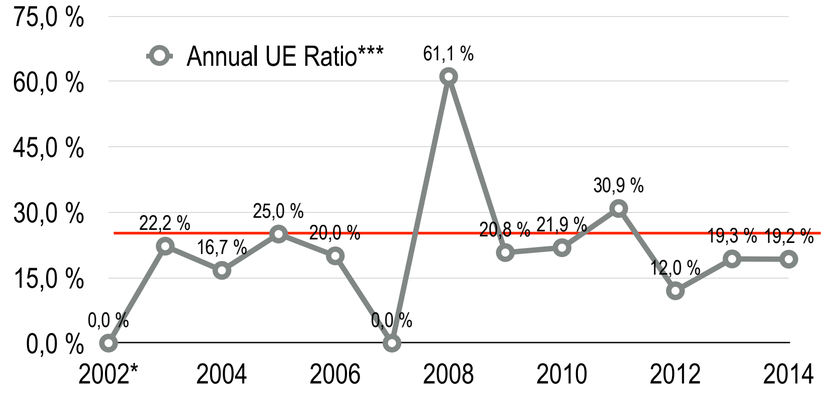
Confirmed Use Errors by Surgical Discipline



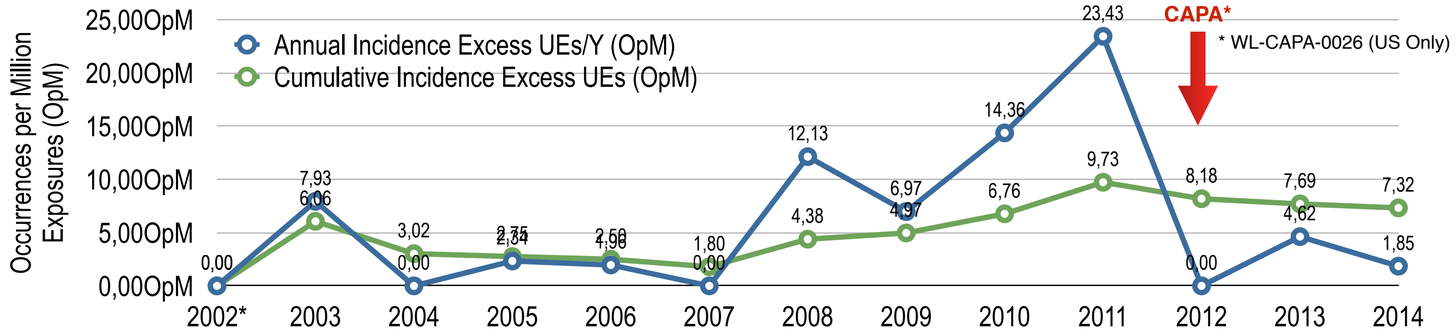
Units shipped/Y Vs. Confirmed User Errors resulting in SAEs



Annual Confirmed User Errors/SAE Vs. Units Shipped



Annual and Cumulative Incidence (OpM) of Confirmed Excess Product User Errors



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2 D. Missing Literature Appraisal

missing or poor appraisal of the clinical literature

Critical appraisal is the process of carefully and systematically examining research to judge its **trustworthiness**, its **value** and **relevance** in a particular context (Burls, 2015).

The appraisal must be **correlated with the device under evaluation**, its mechanism of action, intended purpose, indication for use (clinical circumstances and their severity, exposed patient population) and other state of the art therapeutic alternatives

Source: Burls, Amanda. (2015) "What is Critical Appraisal?" *What is...? series*. Hayward Medical Communications.

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2 Literature Suitability Criteria

Is the selected publication adequate for my purpose?

Suitability Criteria	Description	Grading System (points)
Appropriate device	Were the data generated from the device in question?	D1 Actual device (3) D2 Equivalent device (2) D3 Other device (0)
Appropriate device application	Was the device used for the same intended use (methods of application, etc.)?	A1 Same use (3) A2 Minor deviation (2) A3 Major deviation (0)
Appropriate patient group	Where the data generated from a patient group that is representative of the intended treatment population and clinical condition (i.e. disease, including state of severity)?	P1 Applicable (3) P2 Limited (2) P3 Different population (0)
Acceptable report/data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R1 High quality (3) R2 Minor deficiencies (2) R3 Insufficient information (1)

Source: European Commission. MEDDEV 2.7/1 Rev.4, June 2016. Guidelines on Medical Devices; Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

2 Literature Contribution Criteria

To what extent does publication contribute to the clinical evidence?

Contribution Criteria	Description	Grading System (points)
Data source type	Was the design of study adequate?	T1 Yes (1) T2 No (0)
Outcome measures	Do the outcome measures reported reflect the intended performance of the device?	O1 Yes (1) O2 No (0)
Follow up	Is the duration of follow-up long enough to assess whether duration of treatment effects and to identify complications?	F1 Yes (1) F2 No (0)
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S1 Yes (2) S2 No (0)
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C1 Yes (3) C2 No (0)

Source: European Commission. MEDDEV 2.7/1 Rev.4, June 2016. Guidelines on Medical Devices; Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

2 E. Lack of analysis & evaluation of clinical data

poor analysis of the data in relation to device safety and performance

The unbiased, balanced, critical analysis and evaluation of all relevant clinical data has to provide an amount and quality of clinical evidence to guarantee the scientific validity of the CER conclusions.

What does this data say about the safety and performance of the device under evaluation and have you appropriately incorporated the discussion of every piece of clinical evidence?

Source: European Commission. MEDDEV 2.7/1 Rev.4, June 2016. Guidelines on Medical Devices; Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

2

F. Formalistic Device Risk Management

too focused on conforming with ISO 14971:2019 but no real life use facts

A clinician has to be part of the risk management process, and vigilance and PMS/PMCF data needs to reflect the real life use of the device, beyond conforming to its specifications

Is the manufacturer's risk management able to collect, trend, and interpret all product vigilance and use information to the extent that it provides adequate and sufficient facts to allow for the benefit-risk determination and the acceptability of residual risk?

Source: European Commission. MEDDEV 2.7/1 Rev.4, June 2016. Guidelines on Medical Devices; Clinical Evaluation: A Guide for Manufacturers and Notified Bodies

2 G. Improper Clinical Evaluator

qualification and expertise of clinical evaluator

Clinical reviewer ≠ CER writer

Clinical reviewer approves the CER

Is an active medical professional

- Expert in the specific field of device
- In the clinical area of intended use
- Using device type in daily practice
- Dealing with specific circumstances of use

Has no conflicts of interest - is not:

- The device inventor/developer
- Device clinical trial investigator
- Speaker for device marketing
- Shareholder of the firm

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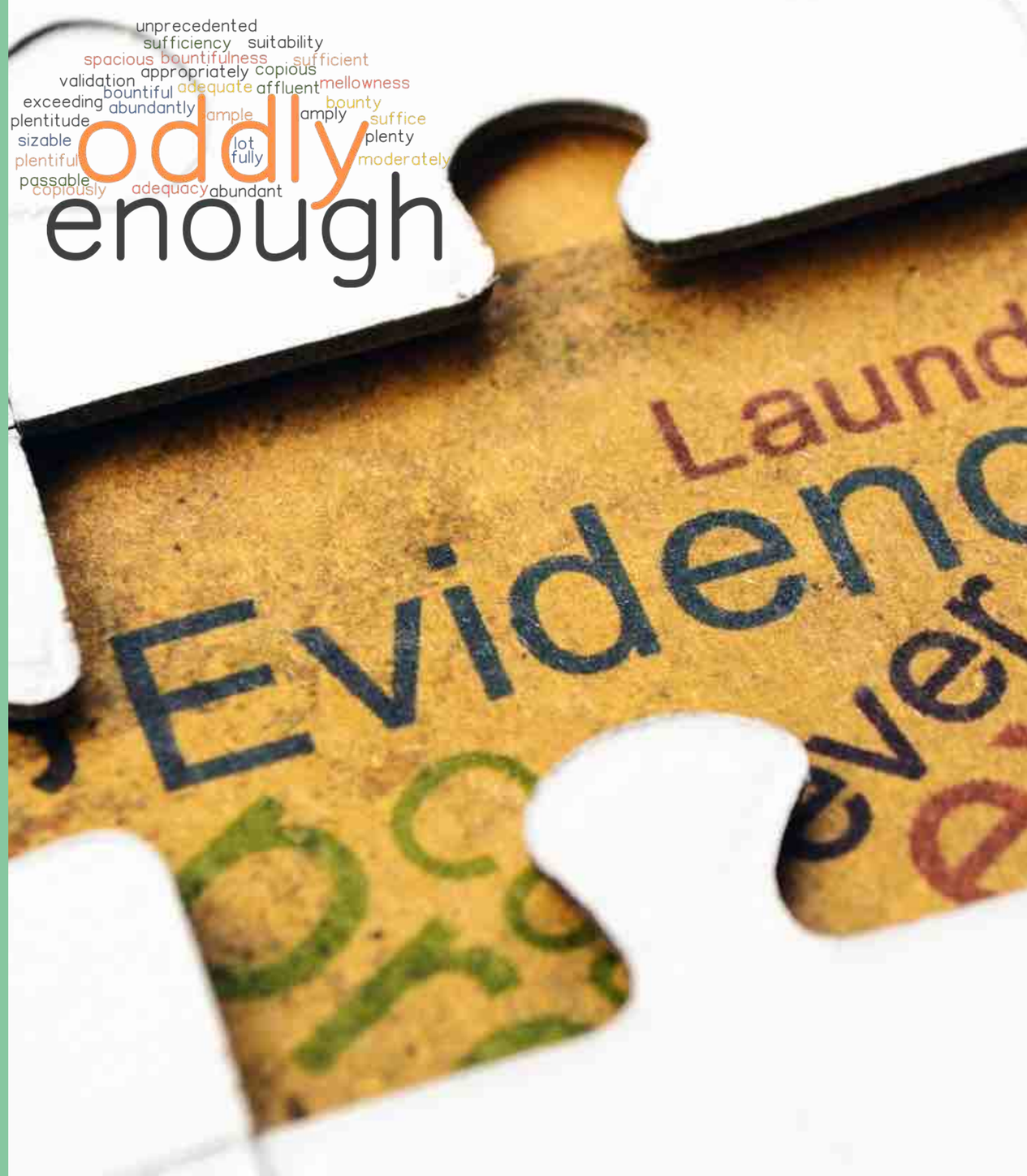
3

CLINICAL EVIDENCE & PMCF

When is clinical evidence sufficient?



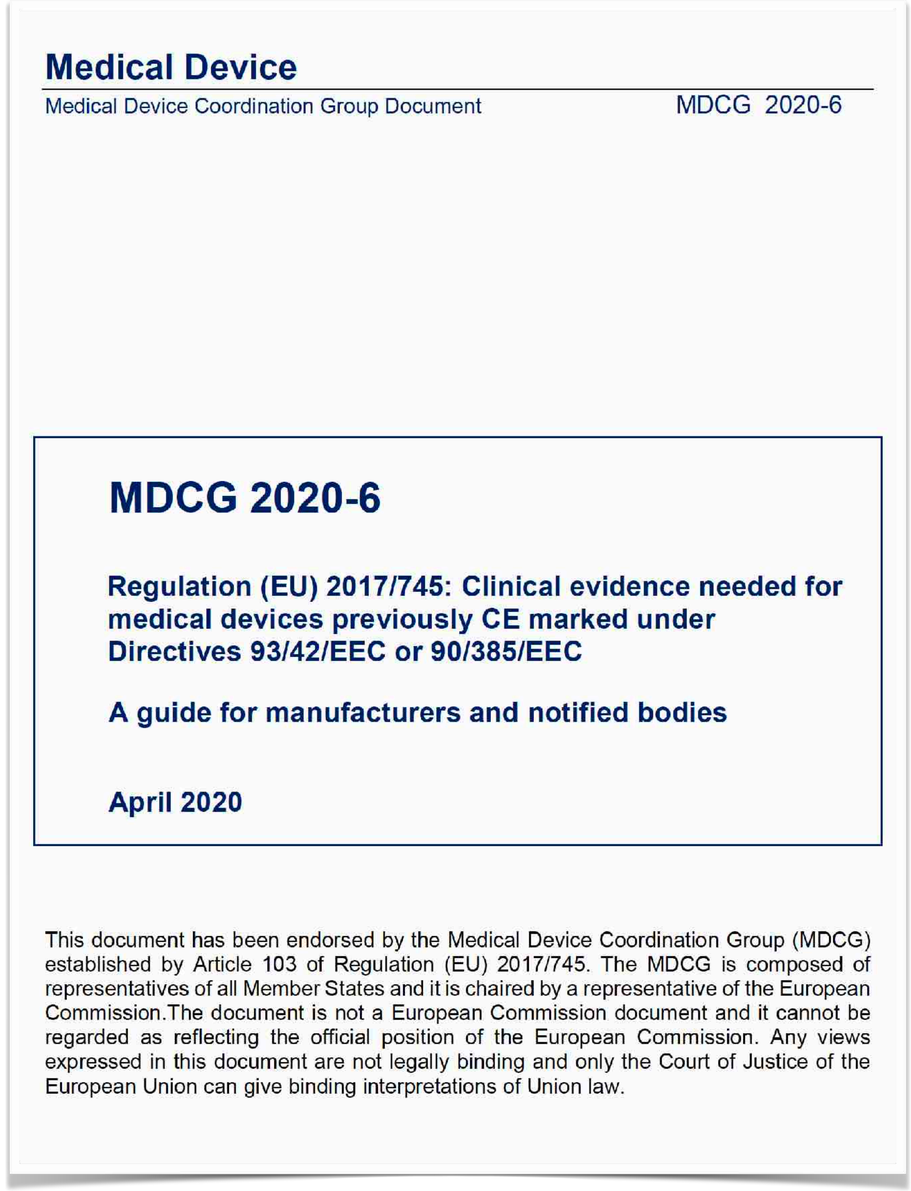
3 What is Sufficient Clinical Evidence?

how is sufficient defined, and by whom?

The requirements of MDR/IVDR are not different from the Directives

Die guidance MDCG 2020-6 Annex III tries to make a clear cut between so-called legacy devices and medical devices that are to be marketed under the new regulation.

With Annex III MDCG 2020-6 one can justify a different (lower) level of data and clinical evidence in order to obtain (re) certification according to MDR.



Medical Device

Medical Device Coordination Group Document MDCG 2020-6

MDCG 2020-6

Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC

A guide for manufacturers and notified bodies

April 2020

This document has been endorsed by the Medical Device Coordination Group (MDCG) established by Article 103 of Regulation (EU) 2017/745. The MDCG is composed of representatives of all Member States and it is chaired by a representative of the European Commission.The document is not a European Commission document and it cannot be regarded as reflecting the official position of the European Commission. Any views expressed in this document are not legally binding and only the Court of Justice of the European Union can give binding interpretations of Union law.

BECAUSE PATIENT SAFETY MATTERS.

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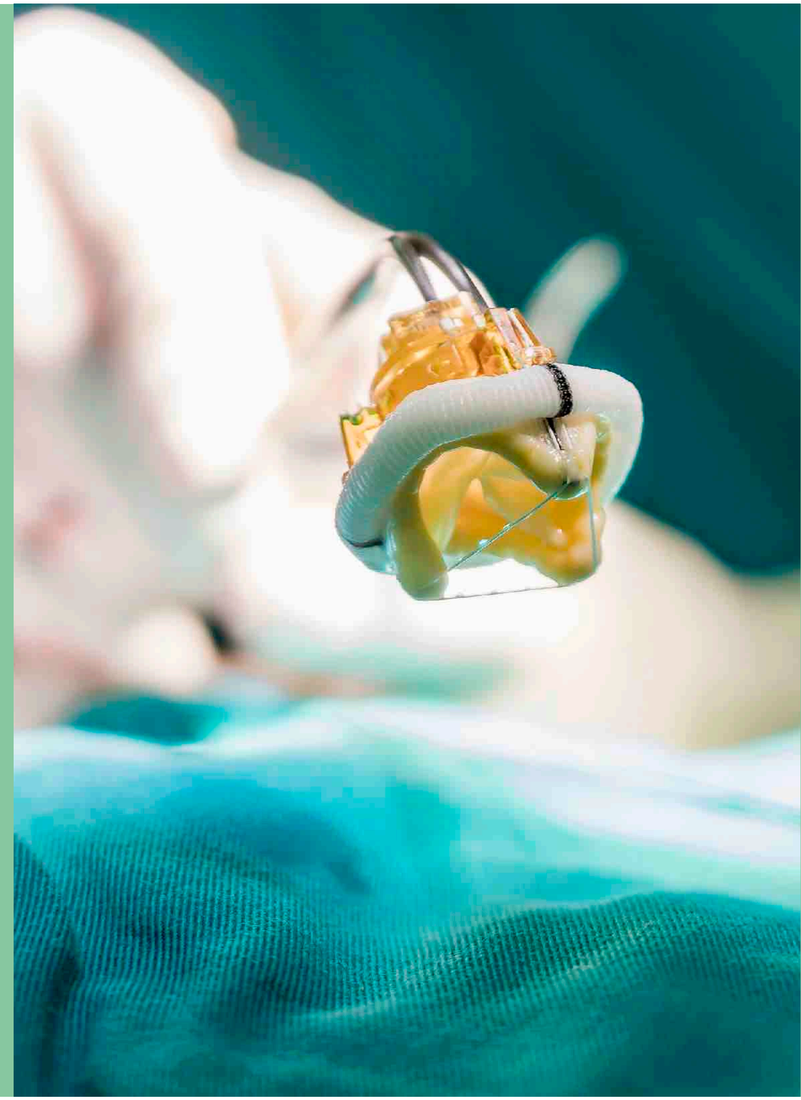
ISO 5910:2018

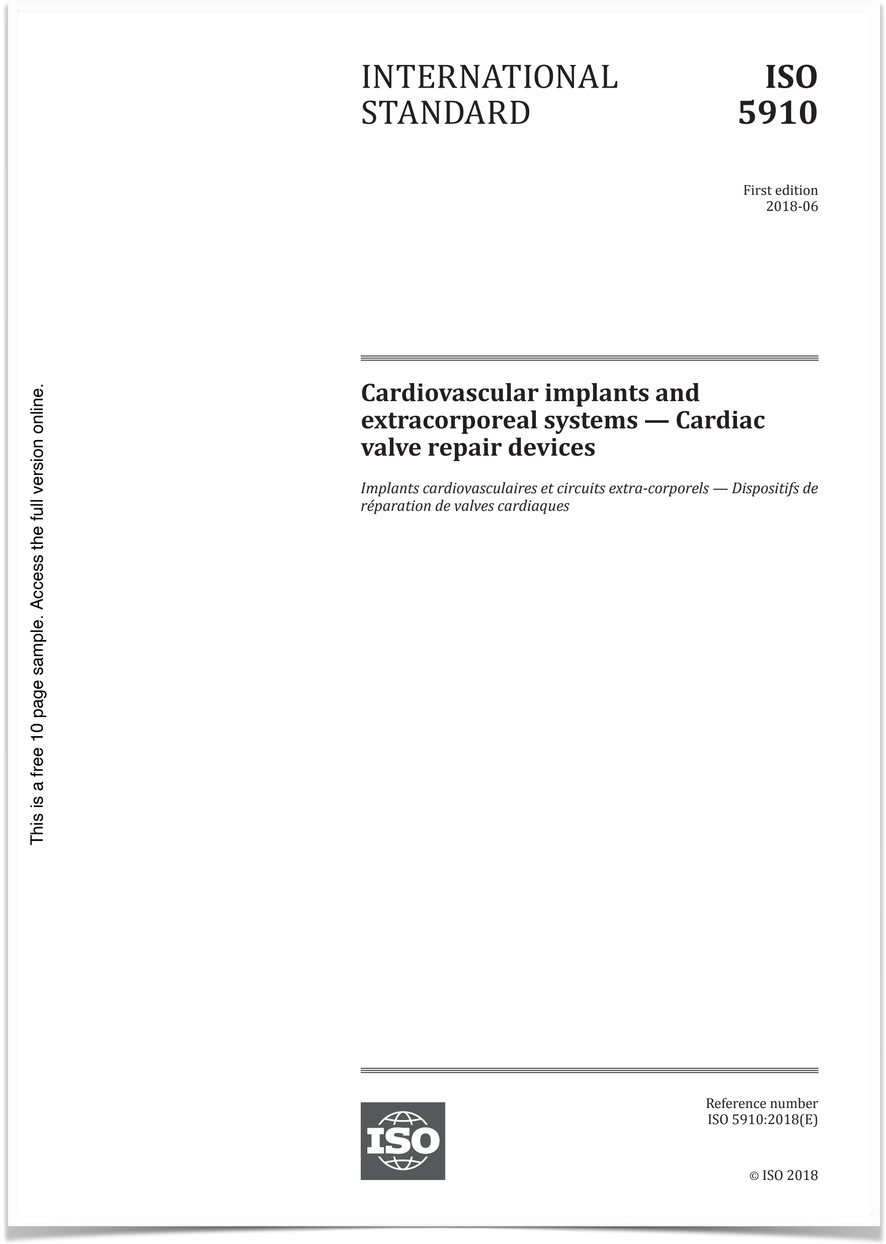
Cardiovascular implants and extracorporeal systems - Cardiac valve repair devices



An Almost Unique Example

ISO 5910:2018

- describes the validation and verification of the design and manufacture of a heart valve repair system through risk management (derived from the risk assessment)
- also the requirements for preclinical in vivo evaluation and clinical testing of the finished heart valve repair system to assess safety and efficacy
- describes exactly the necessary size of the study population, the number of centers required and the years of follow-up



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Still a Dilemma?

Can it work? Does it work? Is it worth it?

Is there something missing here? No, it is unconsciously addressed

1. **Performance:** The ability of a medical device to achieve its intended clinical purpose as claimed by the manufacturer.
2. **Efficacy:** is the extent to which a device does more good than harm under ideal circumstances (“Can it work?”)
3. **Effectiveness:** assesses whether a device does more good than harm when provided under usual circumstances of healthcare practice (“Does it work in practice, under real-world conditions?”)

1. Regulation (EU) 2017/745, Annex I, Chapter I (1)
2. *Haynes B*. (1999) **Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving.** *BMJ*. 1999;319(7211):652-653.

3 Post-Market Clinical Follow-up

proactive collection and evaluation of additional clinical evidence

The manufacturer shall **proactively collect and evaluate clinical data** from the use in or on humans of a device 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.

Annex XIV, Part B

PMCF is rarely supposed to be a clinical investigation
(MEDDEV 2.12/1 rev 8)

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3 PMCF - the Essentials

type of activities and categories of PMCF

1. There are at least four major methodological approaches to PMCF
   - Medical device registry
   - Clinical study
   - Retrospective study
   - Survey
2. There are two categories of PMCF (not specified as such in MDR)
   - General PMCF - compulsory for every manufacturer even if clinical evidence sufficient
   - Specific PMCF - related to studies or registries only, if clinical evidence is not sufficient
3. General PMCF must be conducted without excuses
   - Continuous provision of REAL LIFE CLINICAL DATA to confirm safety and performance in the approved intended purpose
4. Not conducting specific PMCF can be justified by manufacturer when
   - Sufficient clinical data during lifecycle of device
   - No changes in the design, manufacturing and risk profile occurred over time

4 TRANSPARENCY AND DATA ACCESS

Clinical Evaluation Consultation Procedure (CECP)

Scientific Opinion - Intention Vs. Reality

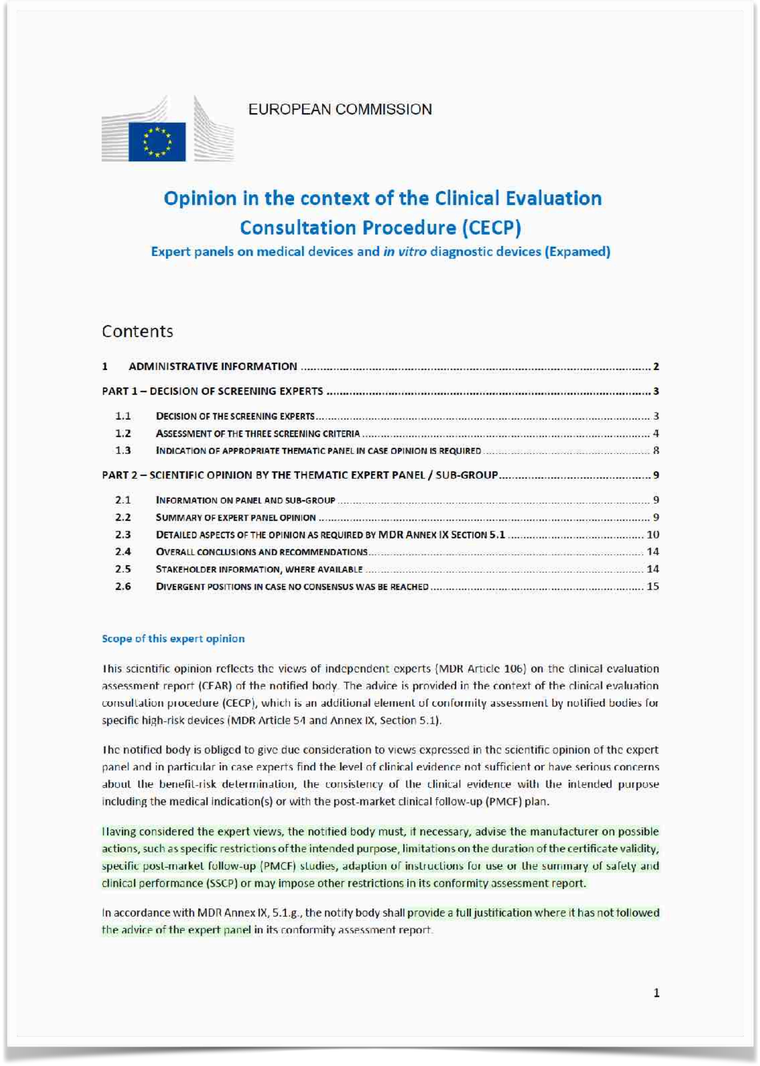
Art.106(12) states the following

The requirements of the MDR/IVDR are clear and unambiguous here

"The **Commission shall publish the scientific opinion and advice delivered in accordance with paragraphs 9 and 11 of this Article, ensuring consideration of aspects of confidentiality as set out in Article 109**. The clinical evaluation guidance referred to in point (c) of paragraph 10 shall be published following consultation with the MDCG."

4 First Expamed Scientific Opinion

acc. MDR Art. 54 and Ann. IX, (5.1) from 21/04/2021



EUROPEAN COMMISSION

Opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and *in vitro* diagnostic devices (Expamed)

Contents

Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the notified body. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The notified body is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow-up (PMCF) plan.

Having considered the expert views, the notified body must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow-up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1

1 ADMINISTRATIVE INFORMATION

Date of reception of the dossier	21/04/2021
Medical device type	Ivory Dentin Graft™ is an implantable device in contact with bone which is mainly resorbed. Ivory Dentin Graft™ consists of porous granules of hydroxyapatite derived from porcine teeth.
Intended purpose	Ivory Dentin Graft™ is a medical device intended to be used as a bone graft material for the repair or augmentation of bone defects in dental procedures.
Risk class / type	☒ class III implantable ☐ class IIb ARMP
Screening step: medical field / competence area	Maxillofacial surgery & Dentistry (devices for dentistry/oral surgery, dental materials etc.) Maxillofacial surgery & Dentistry

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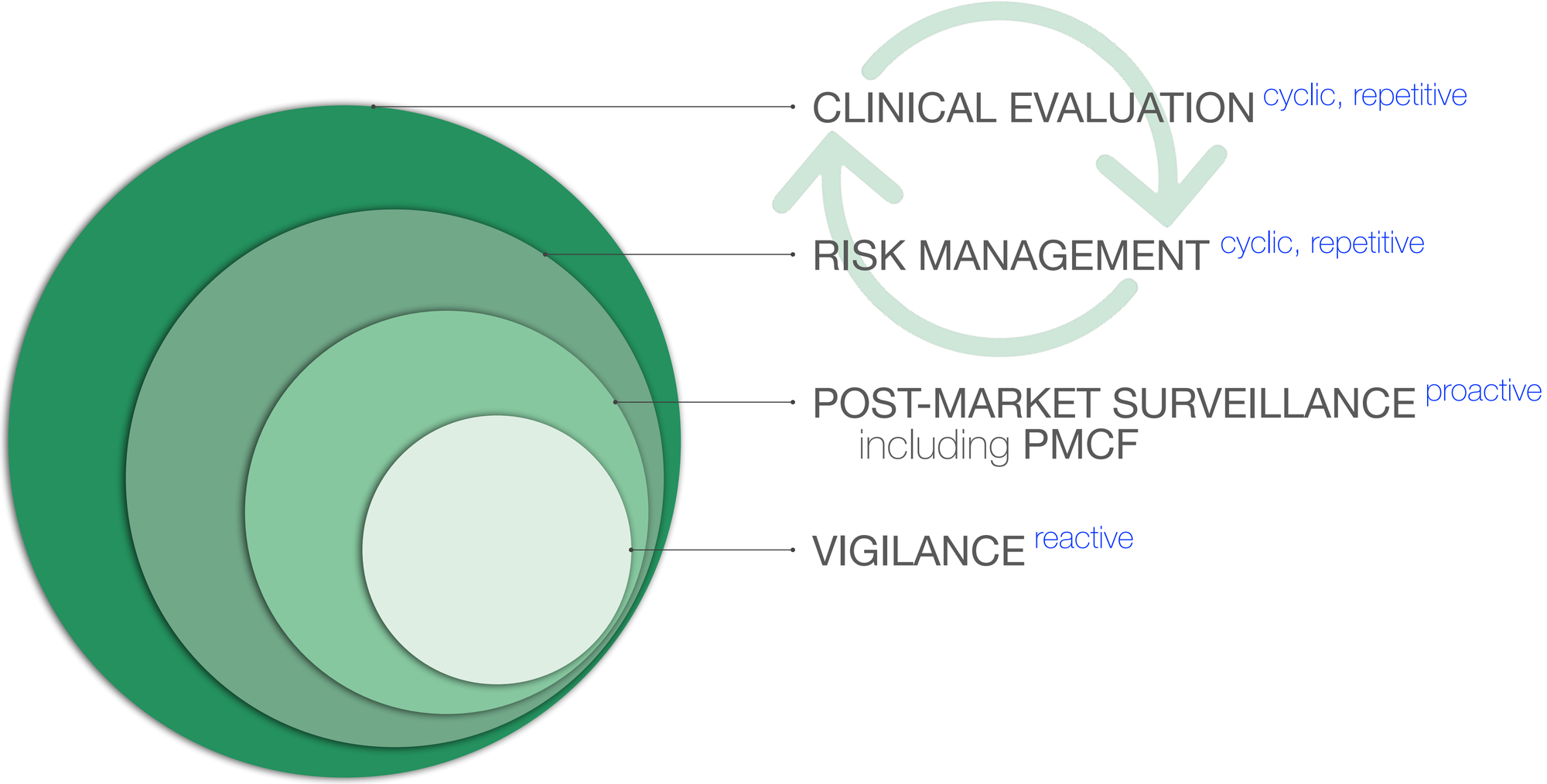
5 CONNECTING THE DOTS

“Read the step. Do the step. Eat the banana.”

Anonymous

MDR Clinical Process Integration

there are four levels of device safety and performance scrutiny



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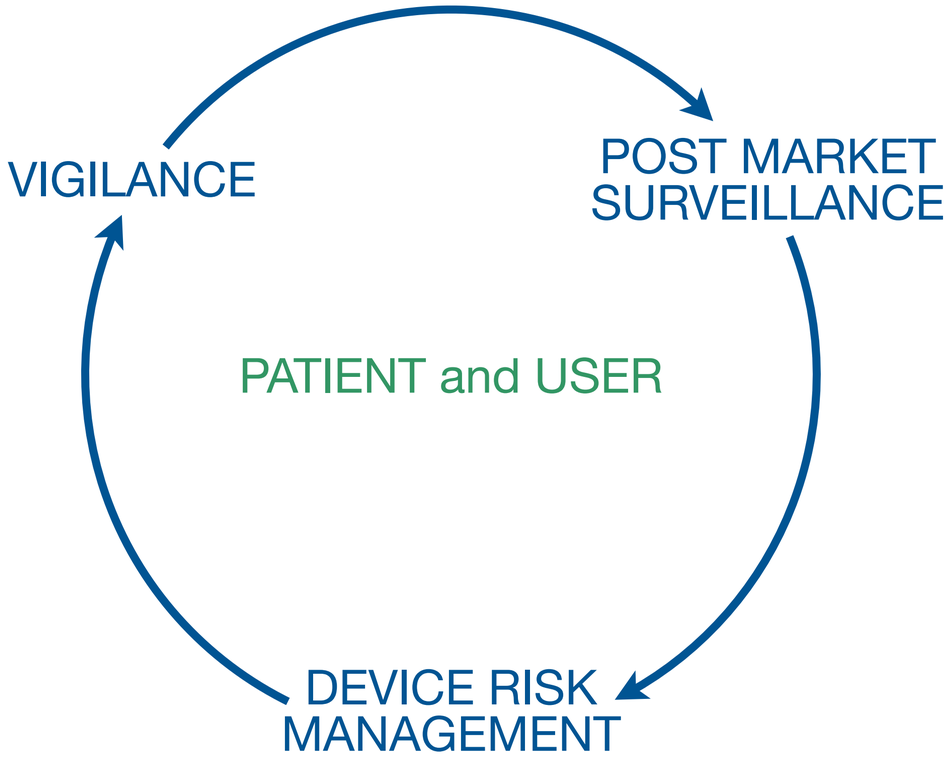
The MDR Strategic Approach

simplifies the complex and is patient/user centric



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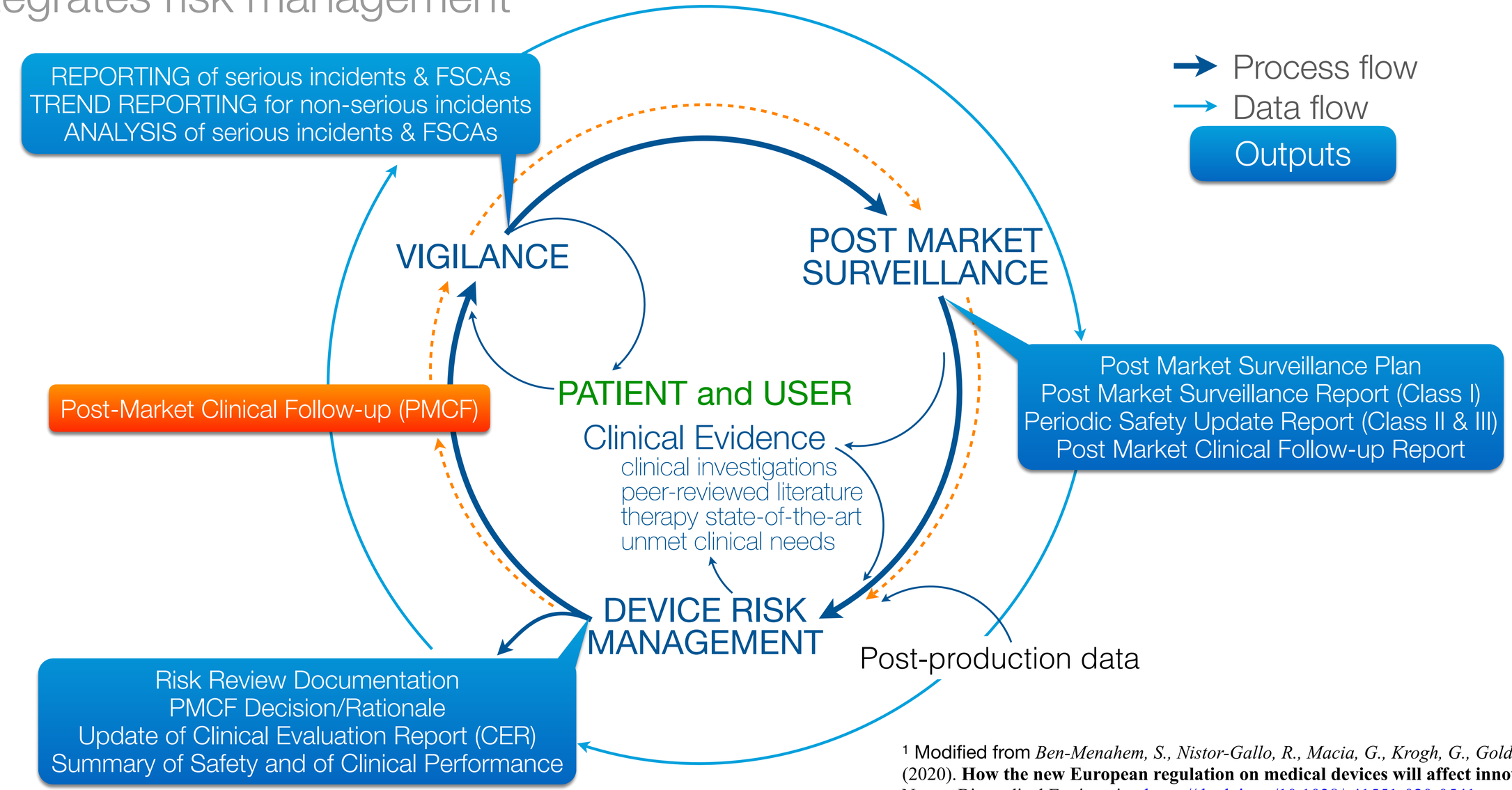
The MDR Cycle[1]

that integrates risk management



[1] Modified from *Ben-Menahem, S., Nistor-Gallo, R., Macia, G., Krogh, G., Goldhahn, J.* (2020). **How the new European regulation on medical devices will affect innovation** Nature Biomedical Engineering https://dx.doi.org/10.1038/s41551-020-0541-x

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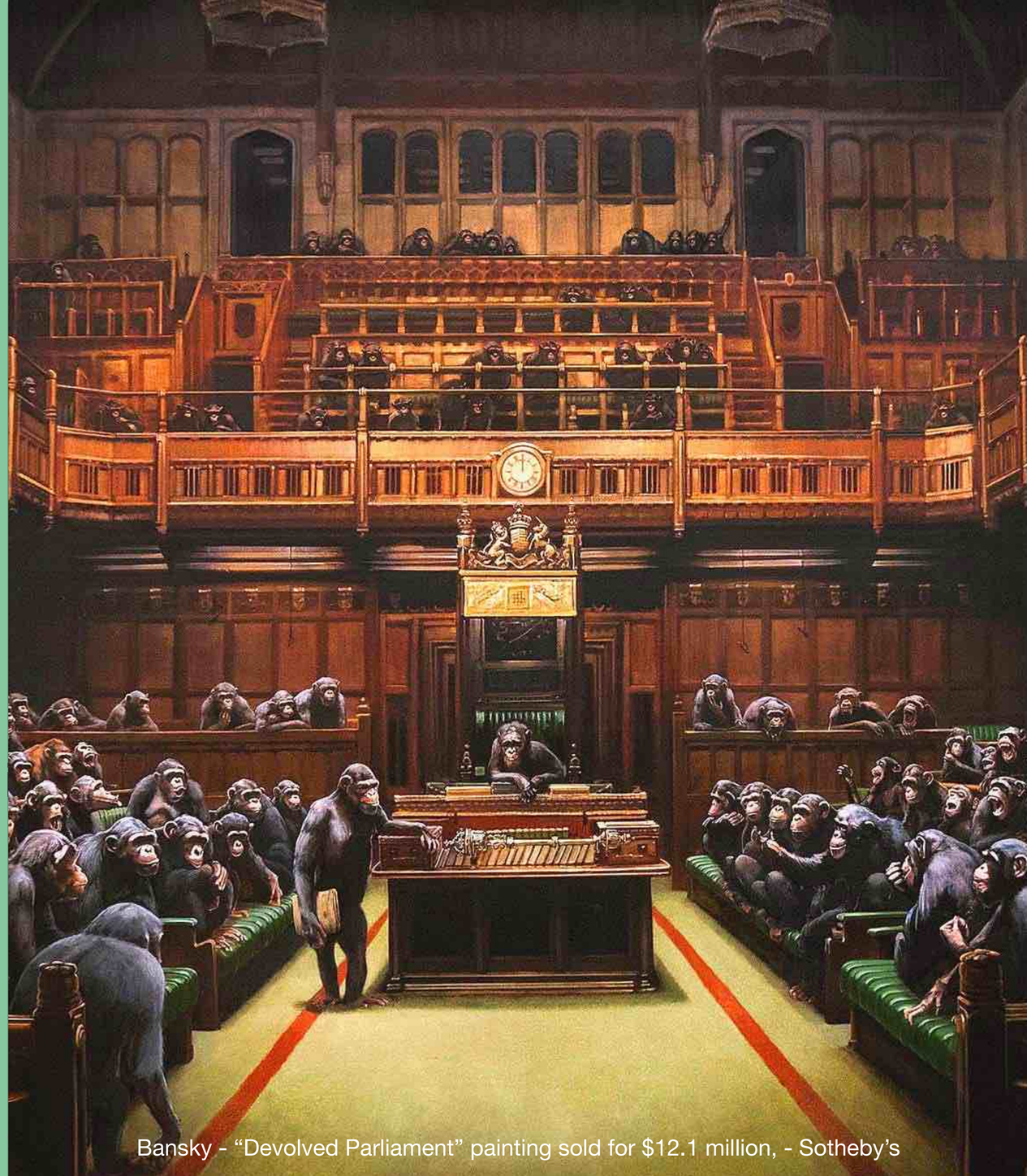
5 ... ONE MORE THING

“We learn from history that we do not learn from history.”

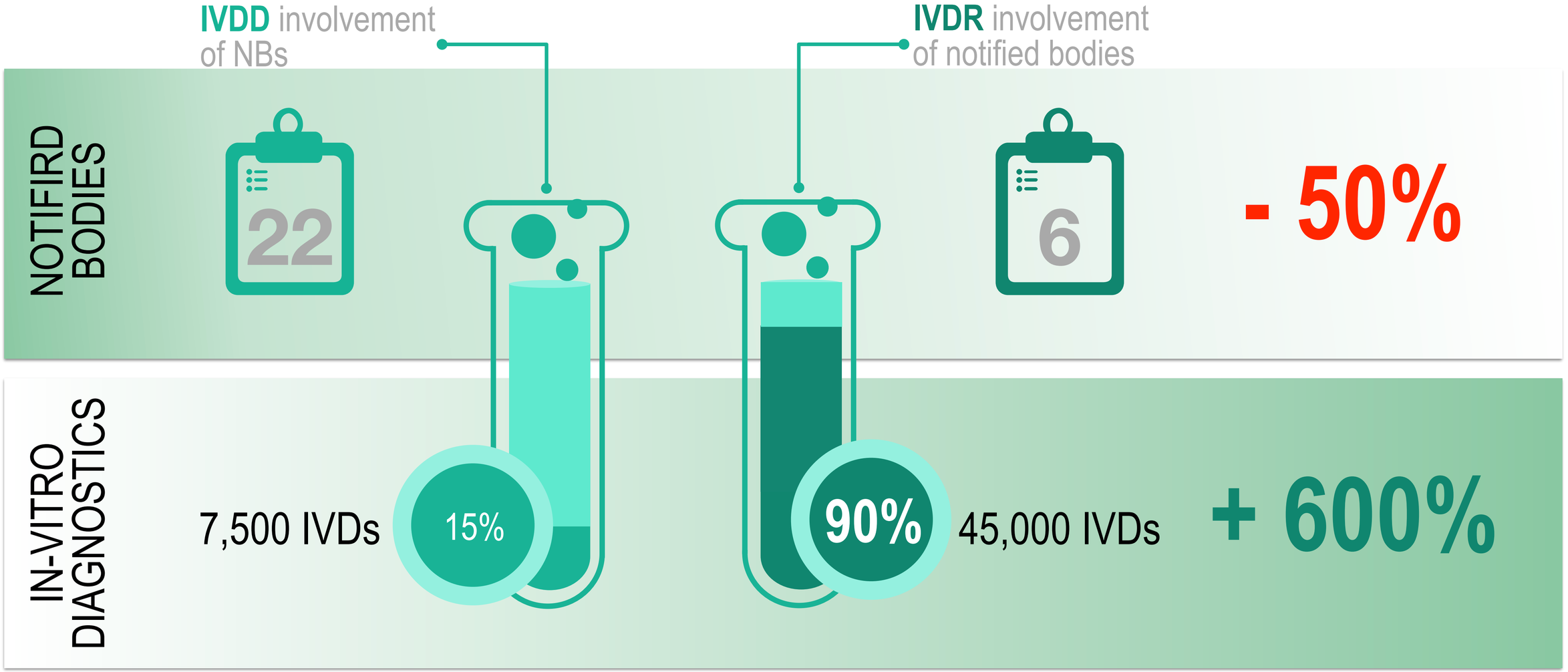
Georg Hegel



Bansky - “Devolved Parliament” painting sold for $12.1 million, - Sotheby’s

IVDR Involvement of NBs*

with about 50.000 IVDs on EU market**



* TÜV Süd Digital Dialog Vol. 2, May, 2021; ** MedTech Europe Market Data In Vitro Diagnostics

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5 Guidances & Best Practices

for clinical evaluation and clinical investigations

Reference	Title	Publication
IMDRF MDCE WG/N56FINAL:2019	Clinical Evaluation	October 2019
MEDDEV 2.7/1rev4	Clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC	June 2016
MDCG 2020-6	Guidance on sufficient clinical evidence for legacy devices	April 2020
MDCG 2020-13	Clinical evaluation assessment report template	July 2020
MDCG 2020-1	Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software	March 2020
MDCG 2020-5	Guidance on clinical evaluation – Equivalence	April 2020
MDCG 2020-8	Guidance on PMCF evaluation report template	April 2020
MDCG 2020-7	Guidance on PMCF plan template	April 2020
MDCG 2019-9	Summary of safety and clinical performance	August 2019
MDCG 2021-20	Instructions for generating CIV-ID for MDR Clinical Investigations	July 2021
MDCG 2021-8	Clinical investigation application/notification documents	May 2021
MDCG 2021-6	Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation	April 2021
MDCG 2020-10/2	Guidance on safety reporting in clinical investigations	May 2020
MDCG 2020-10/1	Appendix: Clinical investigation summary safety report form	May 2020

References

used in this presentation

1. *Ben-Menahem, S., Nistor-Gallo, R., Macia, G., Krogh, G., Goldhahn, J. (2020).* ***How the new European regulation on medical devices will affect innovation.*** *Nature Biomedical Engineering* *https://dx.doi.org/10.1038/s41551-020-0541-x*
2. *Ecker, W., Labek, G., Mittermayr, T. et al. (2020).* ***Clinical Evaluation and Investigation of Medical Devices under the new EU-Regulation.*** *ISBN: 978-3-7519-3766-5*
3. *ISO 14971:2019 Medical devices – Application of risk management to medical devices*
4. *MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software*
5. *MDCG 2020-5 Clinical Evaluation - Equivalence. A guide for manufacturers and notified bodies.*
6. *MDCG 2020-6 Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies.*
7. *MDCG 2020-7 Post-market clinical follow-up (PMCF) Plan Template A guide for manufacturers and notified bodies*
8. *MDCG 2020-8 Post-market clinical follow-up (PMCF) Evaluation Report Template A guide for manufacturers and notified bodies*
9. *MEDDEV 2.7/1 revision 4 (2016) CLINICAL EVALUATION: A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES UNDER DIRECTIVES 93/42/EEC and 90/385/EEC*
10. *REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC*
11. *IMDRF MDCE WG/N56FINAL:2019 Clinical Evaluation*