A clinical academic perspective on the EU medical device regulatory system – how should it evolve?

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Cardiovascular Round Table / Brussels / 17 April 2024

ESC
European Society of Cardiology

“ Regulatory science ”

- **“.. the science of the assessment and evaluation of the safety, effectiveness, potency, quality, and performance of a product ”**

Hamburg MA, NEJM 2010; 363: 2228-32

- **An open and hypothesis-driven collaborative approach to the experimental development and testing, before wide adoption and then critical review, of transparent and evidence-based regulatory policies and procedures .. ?**

Heart valves

Animal models dissimilar from human, insufficiently predictive
Inadequate bench testing of mechanical properties
Incomplete assessment of fluid mechanical properties
Approval of changes as iterative that proved to be substantial

Percutaneous coronary interventions

Clinical application of concept that was not proved
Use of unblinded studies with significant placebo effect
Overuse of equivalence for CE marking without new pivotal trials

Cardiovascular implantable electronic devices

Need for long-term registries conducted independently from industry
Incomplete capture of clinical events by registries with voluntary reporting
Need for rapid and open access to reports of device failures

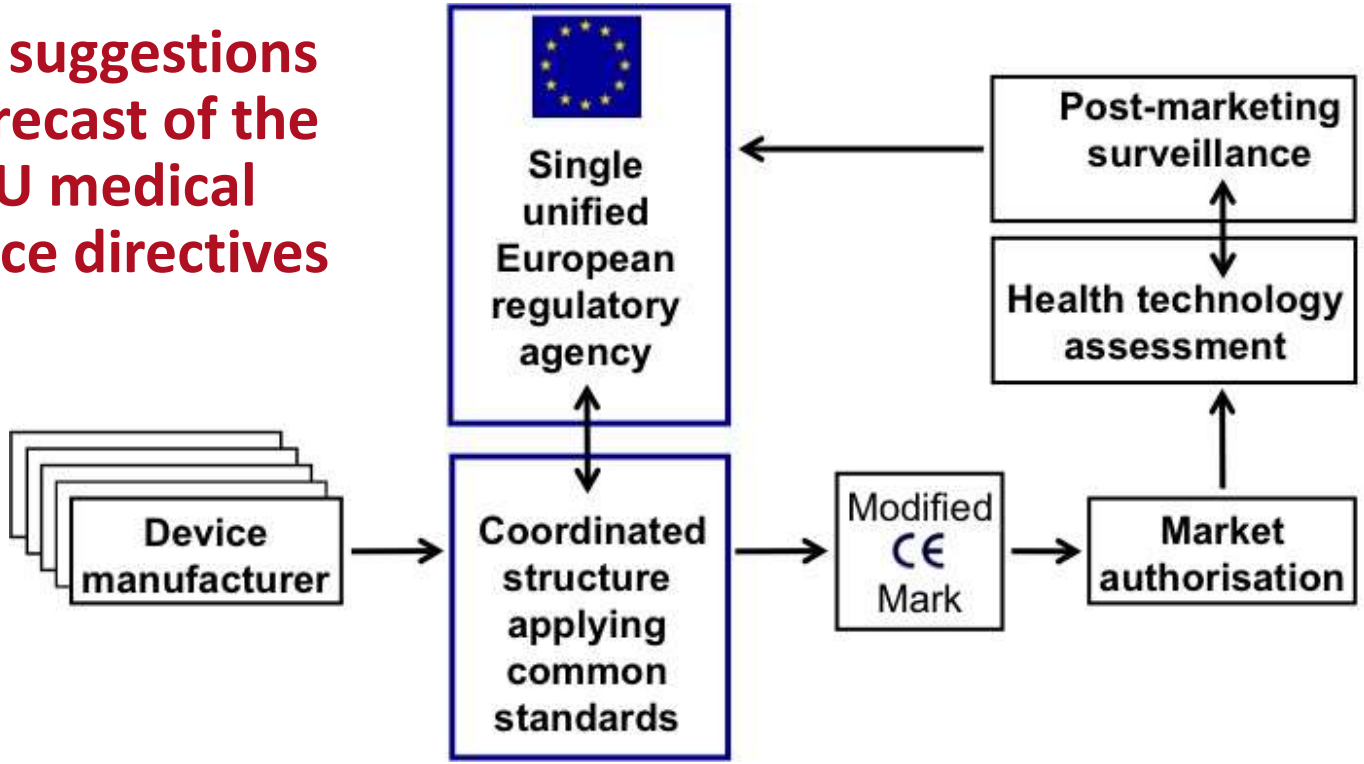
Closure of patent foramen ovale

Early CE marking leading to rapid adoption before proven clinical benefit
Failure by physicians to enrol patients in trials

ESC policy conference

2011

ESC suggestions for recast of the EU medical device directives



Fraser AG et al,
Eur Heart J. 2011; 32: 1673–86

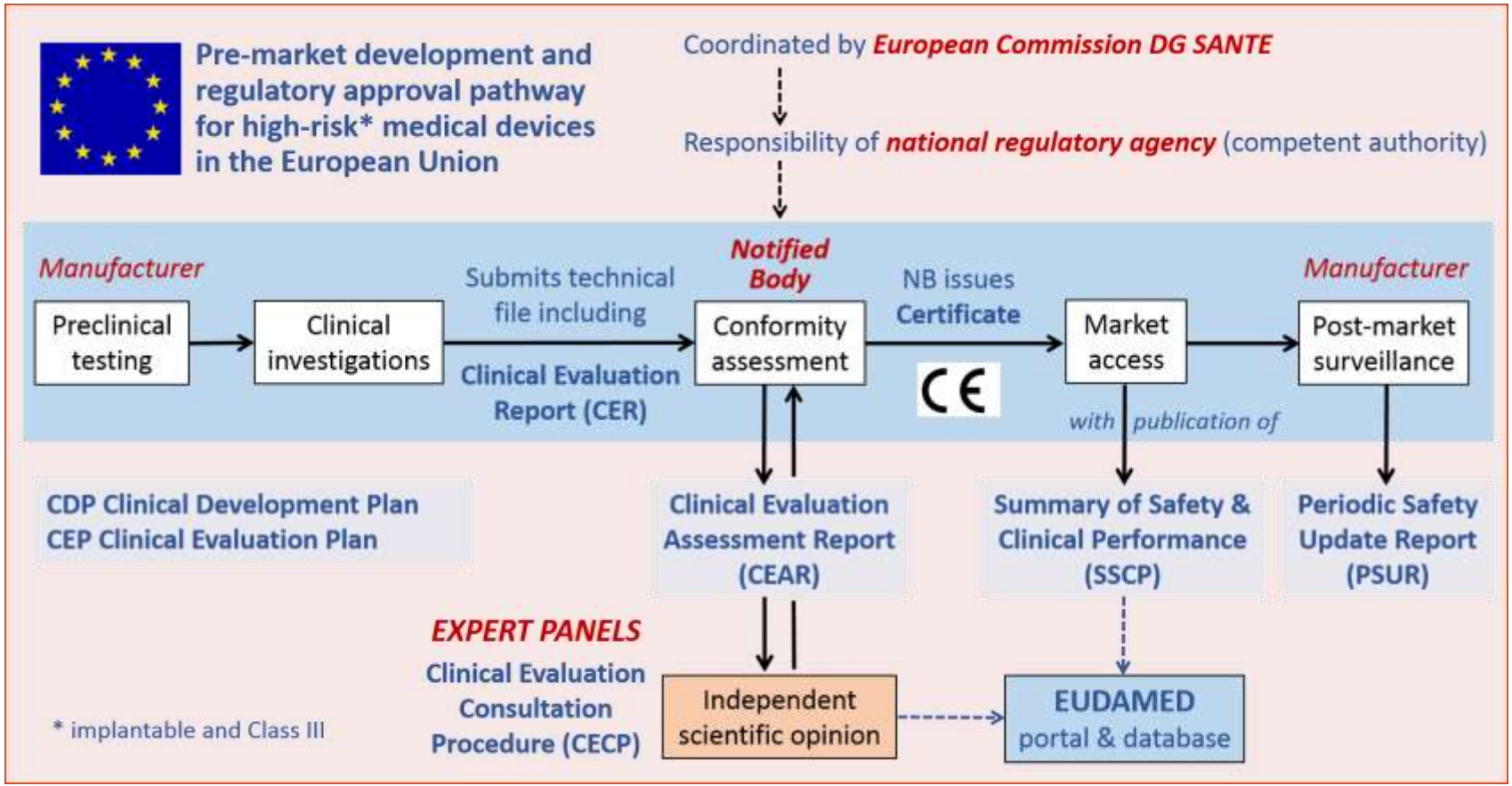
Policy conference, 28th January 2011
Clinical evaluation of cardiovascular devices

European Parliament, Strasbourg, 22nd October 2013

Peter Liese
MEP

Dagmar Roth-Behrendt MEP

Regulation on Medical Devices (EU) 2017/745



Fraser AG et al, Eur Heart J. 2020; 41: 2589–96

Estimated need for EC regulatory capacity and expertise

Impact assessment on the revision of the regulatory framework for medical devices

European Commission, Brussels, 26.9.2012

SWD(2012) 273 final

> The major costs for the EU budget generated by the preferred policy options are linked to the effective management of the future regulatory framework, and in particular to human resource requirements (35 to 50 FTE depending on the option eventually chosen), to the development and management of the IT infrastructure (e.g. Eudamed, ca. EUR 2mio/year) and to meetings between national experts (ca. EUR 1.4mio/year).

https://eur-lex.europa.eu/resource.html?uri=cellar:487acc33-213b-4fdf-bdbb-8840209a8807.0001.04/DOC_1&format=PDF

Concerns about the MDR and IVDR

- **Delays in implementation, lack of capacity**
- **Increased costs and duration of conformity assessment**
- **Uncertainty and unpredictability of evidence required**
- **Over-elaboration?** MDR envisaged 80 tertiary legal acts / now >130 MDCG explanatory and guidance documents
- **Expert panels underused**
- **Delays with implementing EUDAMED, clinical module last**
- **Expected loss of legacy devices**

Examples of statements from SMEs ..

- Company needing new NB had to approach more than 15 NBs
- Costs for conformity assessment have multiplied by 10×
- One company reported paying $ 6,500 per day per reviewer
- Identical sterilization process being reassessed for each device
- > $ 700k already spent without one new certificate being issued
- Certification costs for individual device equivalent to 4× annual sales
- Notified body costs equivalent to 30 – 50 % of turnover
- Only 13% of their products remaining on the market

.. frustration and incomprehension

Gaps in the EU regulatory system

- Few device-specific standards (EU common specifications)
- Insufficient transparency of requirements, and evidence
- No system for early consultation and advice
- No special pathway for innovative technologies
- No special pathway for paediatric and/or orphan devices

(7) The concept of conditional approval of a medical device, pending further clinical evaluation, should be developed

(10) Regulatory systems should retain flexibility for special circumstances

- Limited flexibility .. capacity to be proactive > reactive

EU Medical Device Regulation, Article 121

Evaluation

“ By 27 May 2027, the Commission shall assess the application of this Regulation and produce **an evaluation report on the progress** towards achievement of the objectives contained herein including an assessment of the resources required to implement this Regulation.

Special attention shall be given to the traceability of medical devices through the storage, pursuant to Article 27, of the UDI by economic operators, health institutions and health professionals. ”

Coordination and support action, 1.4.21 – 31.3.24

- Evidence for cardiovascular & orthopaedic devices
- Evidence for devices for diabetes, & for children
- Regulatory guidance on clinical investigations
- Quality of medical device registries

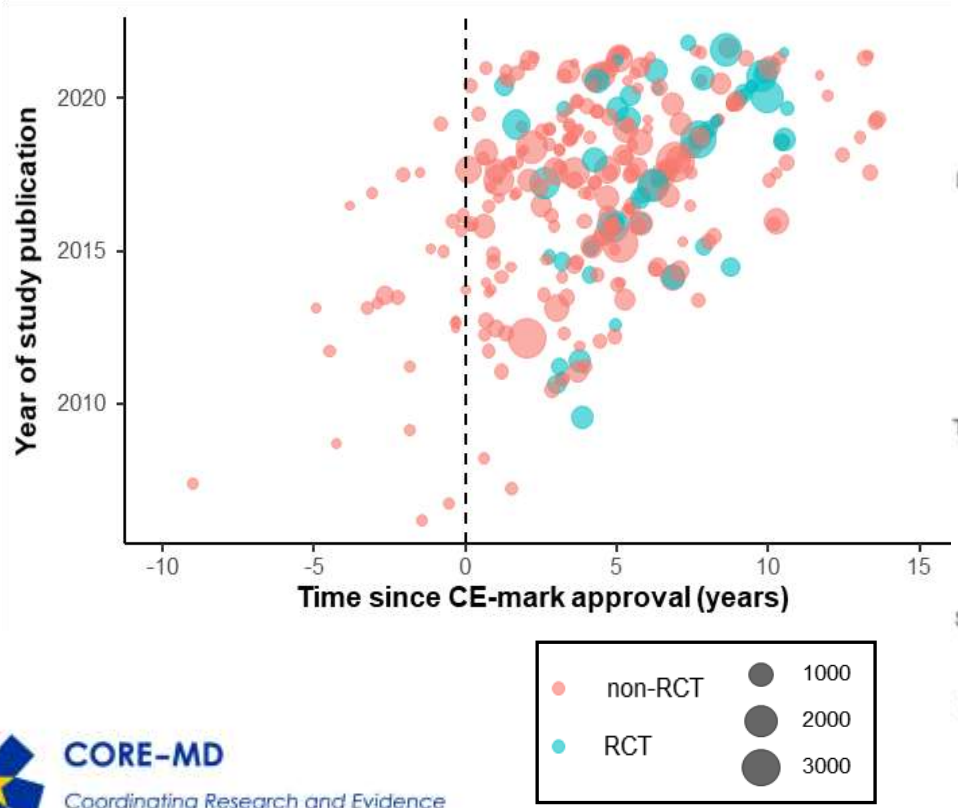
- Statistical tool for risk calculation
- Risk score for evaluation of AI medical devices
- Tool for webscraping safety notices for PMS
- Framework & criteria for device registries
- Recommendations for devices in children
- Code of practice for ethical innovation
- Recommended methodologies for clinical investigations

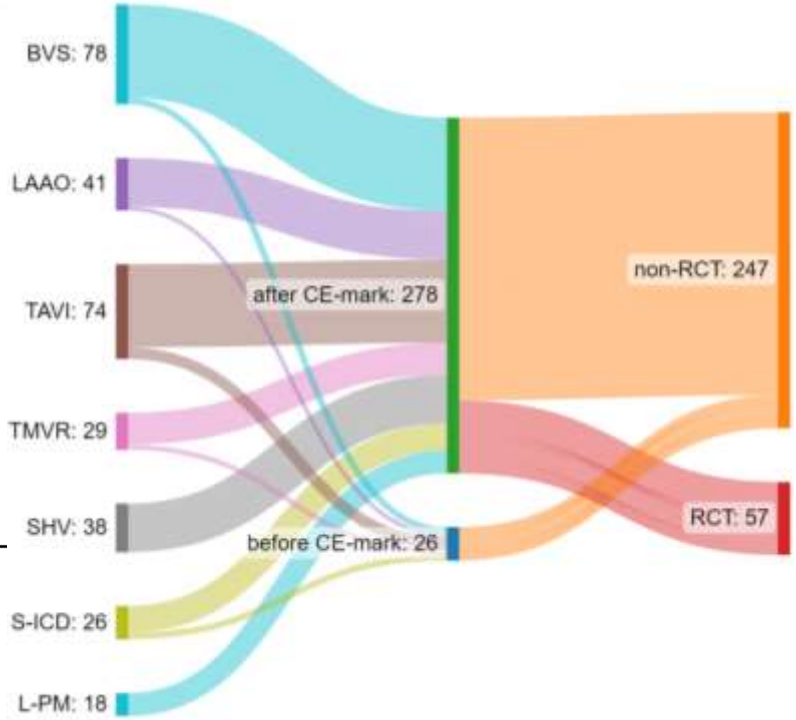
www.core-md.eu/library/

CORE-MD
Coordinating Research and Evidence for Medical Devices

EU Horizon 2020 grant 965246

Systematic review of published clinical evidence for 71 CE-marked cardiovascular devices





CORE-MD
Coordinating Research and Evidence for Medical Devices

Siontis G et al, Eur Heart J. 2024; 45: 161–77

Research, regulatory and clinical decision-making: the importance of scientific integrity

Regulatory integrity

- Over-reliance of small, short trials
- Over-reliance on trials with surrogate markers
- Misapplication of expedited pathways
- Inadequate post-market requirements
- Insufficient regulatory oversight
- Insufficient regulatory enforcement

Wallach JD et al, J Clin Epidemiol. 2018; 93: 88–93

CORE–MD RECOMMENDATIONS FOR STUDY DESIGNS AND METHODOLOGIES

Initial clinical studies	Early clinical studies *	Definitive (pivotal) clinical studies *	Long-term (post-market) clinical follow-up study *
First-in-human and preliminary clinical studies: ***All to be publicly reported.*** • Case report(s) of first implants or other first use of a new high-risk device.[1] • Observational studies assessing feasibility, safety, and early adverse events.[2]	***Assessment of performance, safety, and positive benefit–risk ratio, preparing for later trials powered for efficacy [3]:*** • Observational study (e.g. single-arm, enrolling >150 consecutive patients), using patient-relevant outcomes [i] and/or validated surrogate end-points. [j] • Observational study testing against objective performance criteria (OPCs) [k], with analysis of learning curves. • Case-control or cohort study, assessing differences against another device or current state-of-the-art, and adequately designed to minimise confounding.	***Confirmation of efficacy for clinical outcomes [3], and further demonstration of safety:*** • Double-blind RCT, if feasible. • Single-blinded RCT against active comparator [4] – powered for "superiority". [5] • 'Assessor-blinded' RCT with sham intervention (if no active comparator available). [6] • Single-blinded RCT (as above) – powered for non-inferiority. • Large multicentre observational study, using OPCs or other validated outcome measures.	***Long-term monitoring of device performance and safety, in comparison against alternatives:*** • 'Large simple' RCT such as a registry-based trial. [7] ** • RCT in enriched cohorts. [8] • Well-designed observational study using a registry, or other real-world source of data, including all devices of the same type, and with results combined through a federated analysis, using appropriate adjustments to control for bias if possible.

Example 1: Recommendations for clinical investigations of an innovative or orphan medical device

	Initial clinical studies	Early clinical studies	Rigorous clinical evaluation	Longterm clinical evaluation
Preferred designs	☐ Case report(s) of first implants. ☐ Planned case series with prospective documentation.	☐ Prospective observational study (e.g. single-arm with consecutive patients).	☐ RCT versus current 'state of the art', with blinded determination of clinical end-points.	☐ Mandatory registry.

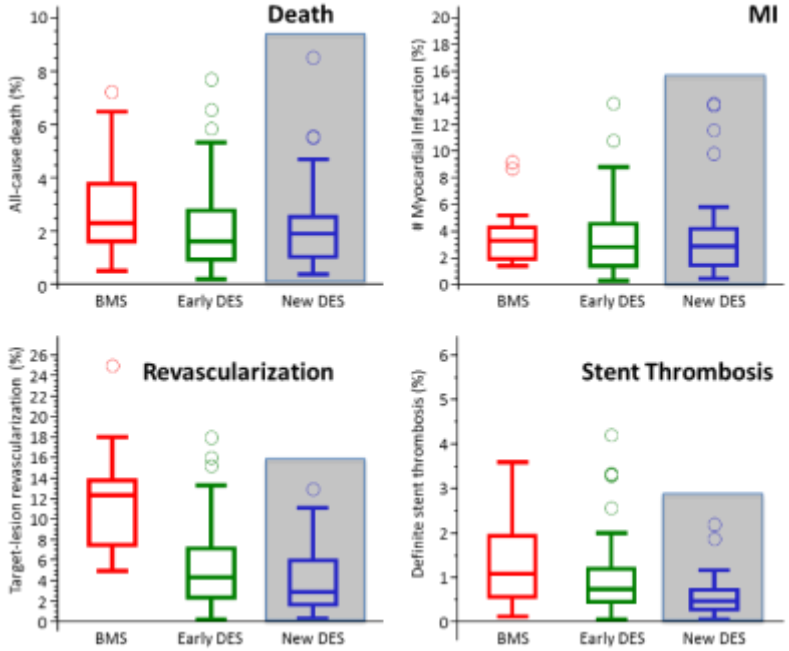
Example 2: Recommendations for clinical investigations of a new medical device in an established class

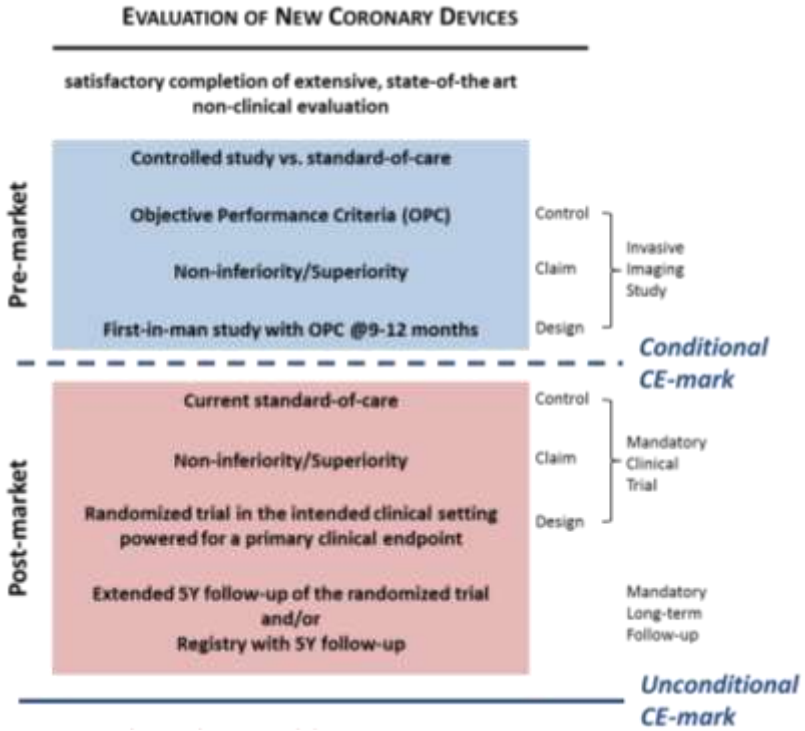
	Initial clinical studies	Early clinical studies	Rigorous clinical evaluation	Longterm clinical evaluation
Preferred designs	☐ Case report(s) of first implants. ☐ Prospective case series.	• RCT with surrogate end-point. • Observational study with objective performance criteria.	☐ RCT against active comparator. ☐ RCT powered for non-inferiority.	• Prospective registry with complete recruitment, recording primary end-points and adverse events.

ESC-EAPCI Task Force on Coronary Stents

EAPCI
European Association of Percutaneous Cardiovascular Interventions

Systematic review of 158 RCTs





Pilot for future interaction with regulators

ESC-EAPCI Stent Task Force
Byrne R et al. | *Eur Heart J* 2015

ESC

BMJ

ESC European Society of Cardiology

Commentary: International collaboration needed on device clinical standards

European Society of Cardiology
American College of Cardiology
World Heart Federation

Patients everywhere should be protected by similar requirements for medical devices to be safe and effective

Fraser AG et al, BMJ 2011; 342: d2952

Medical societies and global convergence ?

IMDRF
International Medical Device Regulators Forum

World Health Organization

GMTA
Global Medical Technology Alliance
Innovating for a Healthier World

DITTA
GLOBAL DIAGNOSTIC IMAGING, HEALTHCARE IT & RADIATION THERAPY TRADE ASSOCIATION

Revolution or Evolution ? / Options to consider ?

- **Accessible standards, EU common specifications**
- **More evidence (from RCTs) for high-risk devices**
- **More flexibility in special circumstances**
- **More transparency / especially for notified bodies**
- **Similar expectations in clinical practice as for drugs**
- **Critical approach to introduction of new technologies**
- **Structural changes, collaborations between regulators**
- *Joint input to EC review from BioMed Alliance and ESC ..*

Advocacy

ESC engagement with European Commission & Parliament

- Scientific advice to DG Research
- European Medicines Agency / HCWP
- Clinical trials legislation
- EU Data Protection Regulation
- Regulation on Health Technology Assessment
- e Health / medical software / radiation protection
- Regulations on medical devices, AI, EHDS ..

Regulatory Affairs Committee, European Society of Cardiology

- Medical Devices Coordination Group
- Working Groups on Clinical Investigation, Surveillance ..
- EU Joint Research Centre
- International Medical Device Regulators Forum
- World Health Organisation