2nd Workshop of the EUnetHTA Task Force on HTA and Medical Devices

Date: May 28th, 2019 in Vienna

Work Package 4
Joint production of Health technology assessments “other technologies”
WP4 Co-Lead Partner: LBI-HTA

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Lead of TF:

1. Claudia Wild (LBI-HTA) – AT (strategic tasks)
2. Petra Schnell-Inderst (LBI-HTA) – AT (operational tasks)

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1. Stefan Sauerland (IQWiG) – G
2. Naomi Fujita-Rohwerder (IQWiG) – G
3. Marina Cerbo (AGENAS) – IT
4. Anna Zawada (AOTMiT) – PL
5. Dominik Dziurda (AOTMiT) - PL
6. Karen Macpherson (NHS Healthcare Improvement) – SCO
7. Ingvil Von Mehren Sæterdal (NIPHNO) – N
8. Chantal Belorgey (HAS) – F
9. Chantal Guilhaume (HAS) – F
10. Hubert Galmiche (HAS) – F
11. François Meyer (HAS) – F
12. Matthias Perleth (G-BA) – G
13. Hannah Brühl (G-BA) – G
14. Nina Egger (G-BA) - G
15. Mirjana Huic (AAZ) – CR
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21. Patricia Harrington (HIQA) – IE
22. Mirella Marlow (NICE) – UK
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24. Frank Hulstaedt (KCE) – BE
25. Mattias Neyt (KCE) – BE
26. Irmgard Vinck (KCE) – BE
27. Heidi Stuerzlinger (GÖG) – AT
28. Gottfried Endel (HVB) – AT
29. Susan Myles (HTW) – UK

Content

Introduction to the Documentation

This booklet documents the 2nd workshop of the EUnetHTA Task Force on HTA and Medical Devices.

The initiative to organize these workshops in 2018[1] and 2019 as an activity of EUnetHTA JA3 WP4 (other technologies) is based on the assumption that with the implementation of the new Medical Device Regulation (MDR) and the In-Vitro-Diagnostics Regulation (IVDR) there is – within the transition period of 3 years (MD) to 5 years (IVD) a window of opportunity to start communication between those institutions responsible for the governance of MDR/ IVDR (the national CA/Competent Authorities supported by the European Commission (DG Grow)), for the market authorization (Notified Bodies/NB) and for reimbursement decision-support (HTA-institutions represented by EUnetHTA).

The **aims of the 2nd workshop** are

1. to get an update on the implementation of the MDR/IVDR as well as on the proposal of the European Commission on a regulation for the European HTA collaboration as basis to explore synergies between regulation and HTA to achieve an optimal evidence generation on high risk medical devices along their life cycle.
2. to provide a platform for views of stakeholders on joint early dialogues, registries and other measures to use synergies between regulation and HTA.

Session 1 "Update: Status Quo of the Implementation of MDR/IVDR and of European HTA. Possible Synergies" is intended to provide the information about the status quo of the MDR/ IVDR regulation and its implementation as well as on the future legal design of European HTA. The speakers point out where they see possibilities for collaboration in the short- and mid-term. This will lay the ground for the presentations and discussions of the perspectives of different stakeholders thereafter.

Session 2 "Perspectives of Different Stakeholders on Collaboration between Medical Device Regulation and HTA. Industry, Payers, Patients and clinicians" gives the perspectives of manufacturers, payers, patients and clinicians on chances and challenges and a possible collaboration in fields with synergies between regulators and HTA agencies on the European level; main focus is on the challenges and synergies for early scientific advice and post-launch evidence generation.

Session 3 "Appropriate Evidence for Regulation and HTA by Early Scientific Advice" will inform about experiences with early dialogues on the European and on the national level. The remit is to show the added value of EDs for all parties and to identify preconditions under which EDs can result in evidence appropriate for regulatory and reimbursement decisions and in an efficient use of resources for all parties.

Session 4 "What is Appropriate Study Design along the Life Cycle of Medical Devices? Clinical Investigations of MDs, Trial designs and Observational Data" presents research on appropriate study designs to evaluate high-risk medical devices along their life cycle.

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[1] The documentation of the 1st workshop May 29th, 2018 can be found here: https://www.eunethta.eu/wp-content/uploads/2018/07/Workshop1_Documentation_05.07.2018.pdf

Agenda of the 2nd Workshop of the EUnetHTA Task Force on HTA and Medical Devices
May 28th, 2019 in Vienna at 8.45- 17.15
Meeting Venue: **Gesellschaft der Ärzte, Frankgasse 8, 1090 Wien**, Room: **Hauptsaal**

Moderated by **Julia Chamova**

8.45-9.15	Registration, Welcome Coffee	30 min
9.15–9.30	Welcome and Introduction to Aim of Workshop Claudia Wild, Director of Ludwig Boltzmann Institute for Health Technology Assessment	15 min

Session 1	***Status Quo of the Implementation of MDR/IVDR and of European HTA. Possible Synergies*** *Presentations*	75 min
9.30-9.50	The EU Legal Framework for Medical Devices: Current Status of Implementation of the Two Regulations. Martin Renhardt, Member of the MDCG, Federal Ministry Labour, Social Affairs, Health, Consumer Protection	
	Q & A	
9.55-10.15	EU Cooperation on HTA beyond 2020 - European Commission Proposal to Strengthen EU Cooperation on HTA. Current Status Quo Orsy Nagy, DG SANTE	apologized
	Q & A	
10.20-10.40	Change of Clinical Assessment by Notified Bodies in the Light of New Regulations Françoise Schlemmer, Hans-Heiner Junker ,Team Notified Bodies	
	Q & A	
10.45-11.15	Coffee break	30 min

Session 2	***Perspectives of Different Stakeholders on Collaboration Between Medical Device Regulation and HTA.*** *Presentations and Moderated Discussion*	**75 min**
11.15-11.30	Perspective of medtech Europe Yves Verboven, Director Market Access and Economic Policies, MedTech Europe	
11.30-11.45	Perspective of Payers (ESIP) Gottfried Endel, Hauptverband der österreichischen Sozialversicherungsträger	apologized
11.45-12.00	Perspective of Patients Valentina Strammiello, European Patient's Forum	
12.00-12.30	Panel Discussion: Questions of Moderator and Audience	
12.30-13.30	Lunch	60 min

Session 3	***Appropriate Evidence for Regulation and HTA by Early Scientific Advice.*** *Presentations and Moderated Discussion*	**60 min**
13.30-13.45	Experience with Early Dialogues on National Level Matthias Perleth, Head of Medical Consultancy Department, Joint Federal Committee, Germany	
13.45-14.00	Experience of EUnetHTA with Early Dialogues for Medical Devices Chantal Guillaume, Haute Authorité de Santé ,	
14.00-14.10	Experience of Manufacturers with Early Dialogues Pascale Brasseur, Health Economics and Reimbursement Director Spine & Biologics, Medtronic	apologized
14.10-14.30	Panel discussion: Questions of Moderator and Audience	

Session 4.1	***What is Appropriate Study Design Along the Life Cycle of Medical Devices? Clinical Investigations of MDs and Trial designs.*** *Presentations*	30 min
14.30 -14.45	The IDEAL-D Concept: Study Designs Along the Life Cycle of Medical Devices Bruce Campbell, The IDEAL Group, Past Chair NICE Interventional Procedures and Medical Technologies Advisory Committees	
14.45-14.55	RCT Designs Developed Especially for the Challenges of Medical Device Properties. Are they used? Stefan Sauerland, Head of Department Non-Drug Interventions, IQWiG	apologized
14.55-15.00	Q & A (understanding)	
15:00-15:30	Coffee break	30 min
Session 4.2	***What is Appropriate Study Design Along the Life Cycle of Medical Devices Observational Data Presentations and Moderated Discussion,*** *Presentations and Moderated Discussion*	**90 min**
15.30-15:45	10-Year Experience in Registries and Big Data for Outcome Monitoring of Medical Devices: Implementation of MR/Meddev 2.7.1, rev4 by NBs, PMCF-design: Which Registry for Which Clinical question? Opportunities for Collaboration with HTA Gerold Labek, Former TÜV SÜD Director Clinical Market Surveillance & Clinical Assessor for Orthopaedic Devices	
15:45-16.00	Global Cardiac Implant Registries: A Critical Analysis. Peter Kolominsky-Rabas, Director, Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health, Friedrich-Alexander-University of Erlangen-Nürnberg,	
16.00-16.15	Implementation of MDR/Meddev 2.7.1, rev4 by Industry, ED and PMCF: Opportunities for Collaboration with HTA Rita Peeters, Sr Director, Regulatory Affairs Policy and Intelligence EMEA Johnson & Johnson	
16:15–16.30	State of Implementation Meddev 2.7.1, rev4 & SSCP and Other Guidelines Tom Melvin, Health Products Regulatory Authority, Ireland Co-chair CIE Working Group	
16.30-17.00	Moderated Panel Discussion: How Can We Use Synergies in the Design of Evidence Generation Between Regulatory and HTA Requirements for Medical Devices? Questions from the Audience	

17.00-17.15	Wrap up and Outlook to Next Activities Claudia Wild, LBI HTA	15 min

Session 1: Status Quo of the Implementation of MDR/IVDR and of European HTA; Possible Synergies.

Minutes Session 1:

1.1 "The EU Legal Framework for Medical Devices: Current Status of Implementation of the Two Regulations" by Dr Martin Renhardt, Federal Ministry for Labour, Social Affairs, Health and Consumer Protection.

Addition/clarifications of the presentation; Q & A:

In every subgroup only stakeholders are allowed. Stakeholders are neither in the Notified Bodies oversight subgroup nor in the surveillance subgroup.

Q: Which stakeholders are allowed as observers? It seems that HTA is not considered as a stakeholder.
A: Industry representatives are allowed. There was no discussion whether HTA is considered as a stakeholder or not, this discussion should be brought to the European Commission. Only European associations are allowed to meetings. DG SANTE participated in those meetings.

Q: Who is in the expert panels? Are patients represented in the expert panels?
A: Expert panels are set up by the European Commission. The Joint Research Centre considers the applications. There will be a call for experts after the implementation act and it is foreseen that medical experts in connection with high-risk medical devices will be in the panels. Specifics for the expert criteria still need to be defined. Experts will not be from associations; they will participate as individuals. There will be 11 or 12 expert groups (e.g. cardio). Caveat: not yet final. Call for experts should be this autumn. Might be done similar to how EMA is looking for experts (then having conflict of interest assessed etc.)

Q: The plan was to reduce the number of Notified Bodies, to harmonise the quality criteria to become a Notified Body and to ensure that they are more homogenous. The presentation seems to give the impression that the European Commission wants as many Notified Bodies as possible. What kind of number is expected and what is the expected standard quality criteria for Notified Bodies?
A: Up to now, 47 applications have been received. It is not the plan to have as many Notified Bodies as possible. When looking at the procedure it takes 1.5 years from starting the application to the designation. There is a danger of not having enough Notified Bodies for May 2020.
It is a European procedure and it is much stricter than in former days; it is laid down in the regulation and it is transparent. Ca 20 Notified Bodies are expected by the end of the current year.

Q: Where do you see possible cooperation/synergy between HTA and the regulation of medical device access to the market?
A: With clinical evidence evaluation - it is a question of linking the processes. Current situation: conformity assessment/CE mark, then assessment. Processes should be linked more, but still stay separate.

1.2 "EU Cooperation on HTA beyond 2020 - European Commission Proposal to Strengthen EU Cooperation on HTA. Current Status Quo." Read by Claudia Wild as DG SANTE was unable to attend.

Addition/clarifications of the presentation; general discussion (Q& A):
Some possible synergies are noted, who will be responsible to coordinate this to avoid fragmentation? Who will do that? Question of "how" needs to be clarified as well.

Q: There is a need for clarification of what the role of HTA is and where it could be in the approval process. A risk is perceived that HTA comes at the end of the approval process and it is not clear what needs a scientific expert opinion. It is worrying that HTA is not involved in the expert panel, just comes afterwards. Who is in the expert panel? Therefore, there is a risk that HTA will not be considered.
A: The criteria for the expert panel is being revised, this seems to be the right time for the HTA community to get their voices heard. It is important to have clarity on the governance, government processes of different unions and to educate on what is needed for the structure of the medical devices regulation (MDR).

Q: What is the timeline? There might be some delays? Regulation is looked after by DG SANTE. DG SANTE has limited resources. Need to have more attention from HTA community on this. What are the formal requirements that need to be in place for the MDR? How does Claudia Wild envision the HTA community to work in the future? Work together even if no formalised system in place?
A: In Austria LBI-HTA assesses 15 high risk hospital interventions per year. In Germany 40-45 new devices reach the market. DG SANTE will support the management function in coordinating assessments. LBI-HTA as national agency will continue doing collaborative assessments in medical devices (MD). In EUnetHTA 6 Activity Centres have been set up that provide the project management in MD, those are the ones who keep on doing project management.

1.3 "Change of Clinical Assessment by Notified Bodies in the Light of New Regulations" by Francois Schlemmer and Hans-Heiner Junker, Team Notified Bodies.

Addition/clarifications of the presentation; Q & A:

- NB-Med will be NBCG Notified Bodies Coordination Group (according to new regulation)
- Important changes and improvements: 1 European database (not national registries), implant cards will be harmonised. Real life use of devices.
- GSPR: General safety and performance requirements and Notified Bodies just check if the product is in compliance with the MDR and the general safety and performance requirements are fulfilled. What is state of the art? It is harmonizing standards, but we do not have harmonised standards for the MDR and it will take years to achieve that. Many of the changes in the MDR are linked to clinical data. In the future a manufacturer can compare their device only to a single device if they want to use the equivalence approach (from own company or competitor).
- SSCP= summary of safety and clinical performance report

- TEAM NB is a voluntary association of Notified Bodies. Not all Notified Bodies are involved.
- NBRG= Notified body recommendation group: aim is to draft the guidances.
- PMCFR= Post market clinical follow up report.

Q: What is the work force planning? There are rumours of shortages, manufacturers having to withdraw products?
A: MDR is requiring more input/resources on the one side and manufacturers have to consider how they fulfil the new requirements. They might find that they do not have enough data on a product – they then could decide that they do not bring the product to the market. It is too early to say now how many Notified Bodies will be designated and if this will affect products getting to the market. Currently it is still not clear if there will be enough Notified Bodies to meet the requirements of manufacturers.

Q: There is a hard deadline for high-risk medical devices. For class III devices, there is a concern about a possible delay of designation. Notified Bodies need to monitor what manufacturers are doing. If a manufacturer is well prepared, the time investment from the side of the Notified Body can be reduced and the process will be faster.
A: Plan A - most manufacturers can be certified before May 2020; Plan B - some can be certified after May 2020. It is assumed to have 12-13 Notified Bodies by the end of the year, the European Commission is more optimistic (they expect to have 20 Notified Bodies until the end of this year). By May 2020 there will be 50% of Notified Bodies that have existed before. Many changes occurred which requires a lot of resources from the manufacturers' side. Some manufacturers have started to prepare for the MDR only now which is late as it takes some years to adapt to the required changes. Some medical devices will probably disappear from the market if the manufacturers have not started to prepare for the MDR so far and maybe for some products it is not in the interest of the manufacturer to go through the certification procedure for a product which is already on the market for a long time (or if only a limited number of devices is sold per year, it is not worth the effort).

Q: Many devices will be upgraded, do you know the number (%) of class I devices which will be upgraded? Many products need Notified Bodies certification/reclassification after May 2020.
A: No specific numbers, only speculation. There will be many products that need reclassification in the future. Currently almost all software is class I - according to MDR these will be reclassified.

Q: Who will do what with which skills? Manufacturers need to do more and deliver the data. Really just one side of the coin? Do Notified Bodies have the skills to cover all of this (check literature search, appraise literature etc.)?
A: The manufacturer is responsible for being compliant with the regulation. The Notified Body is independent. Manufacturer has to provide everything that is needed for evaluation. Manufacturer needs to have qualified staff, to write the report. Notified Bodies have medical doctors as employees, also have contracts with external medical doctors. Notified Bodies have to have (similar to the manufacturers) qualified personnel. At the moment it is a race, where experts can be found.
Beyond clinical experts, others like statisticians, information specialists, methodological experts might be needed as well.

Q: NBCG (Notified Bodies Coordinating Group) – who can be the members? Are stakeholders represented? Observers?
A: MD-med changed the rules 2 years ago. It is a closed session where only Notified Bodies are allowed. There is an open session where there stakeholders can attend (European stakeholders i.e. associations that are representing national stakeholders, they are not looking for national organisations). European HTA organisations could be invited as well.
Hans-Heiner Junker, representative of Team Notified Bodies offered to arrange that an HTA specialist can speak about HTA at the NB meeting (to explain what HTA is etc.)

Q: Any other possibility for cooperation?
A: Notified Bodies might not understand the criteria that HTA is working with. Notified Bodies have criteria defined in MDR. First we should define where there are possible synergies between HTA and Notified Bodies to be able to work together.

Comment: It was suggested that coverage with evidence, real world evidence could be areas where the Notified Bodies and HTA could cooperate. Other possible collaboration: horizon scanning (EUnetHTA work) or special access (where you can use a technology without being assessed) - to prevent loss of innovation from start-up companies.
A: There are 10-14 people in an audit team at a Notified Body. Notified Bodies need to have a qualification system in place – to do the job as an expert, or auditor. Notified Bodies cannot subcontract parts of an assessment to another company, they can only have single persons under contract, who are individuals.
Comment: The criteria should be known as HTA experts are not intending to interfere in Notified Bodies´ work, but would just give advice, which qualifications/skills Notified Bodies would need. Then Notified Bodies do their work without interference of others.

Comment: If HTA wants to be involved as an expert, it would be as individual experts. If HTA defines the role as an expert organisation – their role is limited to support guidelines. Work of Notified Bodies is confidential. If looking for cooperation, role needs to be defined.

Comment: There could be a dramatic discrepancy between indications mentioned in a CE mark and clinical indications. You see very broad indications from manufacturers, but very narrow reimbursement decisions due to HTA. A place for Early Dialogues (EDs) is seen when technologies are being approved.
A: Competent authorities make the role of Notified Bodies clear. The manufacturer does the design and engineering activities with the application. The Notified Bodies assess the design of the devices; the role of Notified Bodies is at the very end. It would be good if Notified Bodies could discuss at the beginning what is needed, but they are not allowed. Notified Bodies are not allowed to consult, to tell the manufacturers what they need to do in order to get an approval. Notified Bodies need to be independent so they can only advise on the requirements, not how to meet the requirements.

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EUnetHTA Task Force on HTA and Medical Devices – Workshop 28.5.2019

The EU Legal Framework for Medical Devices: Current Status of Implementation of the Two Regulations

Dr. Martin Renhardt
Dep. VIII/C/1
Vienna, 28. May 2019

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Implementing Act – Notified Bodies

- Defining the list of codes and corresponding types of devices for the purpose of specifying the scope of the designation of notified bodies
- Adopted and published on 24 November 2017
- Essential pre-condition for the launch of the designation procedure for Notified Bodies

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Common Specifications for products without a medical purpose

- Common specifications (CS) addressing for any of the groups of products listed in Annex XVI of the MDR, at least, application of risk management as set out in Annex I and, where necessary, clinical evaluation regarding safety.
- Application of MDR to Annex XVI products depends on the adoption of CS
- Expected quarter 1/2020

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Setting up of Expert Panels

- Making provision for expert panels to be designated
- Based on this implementing act, the selection of experts will be carried out
- Expert panels are tasked inter alia with the delivery of opinions on the clinical evaluation of certain high-risk devices in the context of the premarket scrutiny
- Tasks of expert panels are described in Article 106 (10)
- Draft implementing act in preparation – expected quarter 3/2019

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Fees for expert panel services

- Implementing Act
- Definition of fees for the advice provided by expert panels
- Survey with MDCG members and stakeholders finalised. This is intended to support the drafting of the future act
- Expected quarter 4/2019

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Notified Bodies Designation

- Designation of Notified Bodies under the Regulations is a pre-condition for carrying out of conformity assessment
- 47 applications received by the commission services, 26 joint assessments carried out and 7 more already scheduled.
- Full scope of MDR and IVDR covered in the applications
- As many Notified Bodies as possible designated prior to May 2020

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MDCG subgroups

- WG 1 Notified Bodies Oversight (NBO)
- WG 2 Working Group on Standards
- WG 3 Working Group on Clinical Investigation and Evaluation (CIE)
- WG 4 Working Group on Post-Market-Surveillance and Vigilance (PMSV)
- WG 5 Working Group on Market Surveillance
- WG 6 Working Group on Borderline & Classification

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MDCG subgroups

- WG 7 Working Group on New Technologies
- WG 8 Working Group on Eudamed
- WG 9 Working Group on Unique Device Identification (UDI) & Device Traceability
- WG 10 Working Group on International Matters
- WG 11 Working Group on In Vitro Diagnostic Medical Devices

MDCG Subgroups operational as from 1st March 2019

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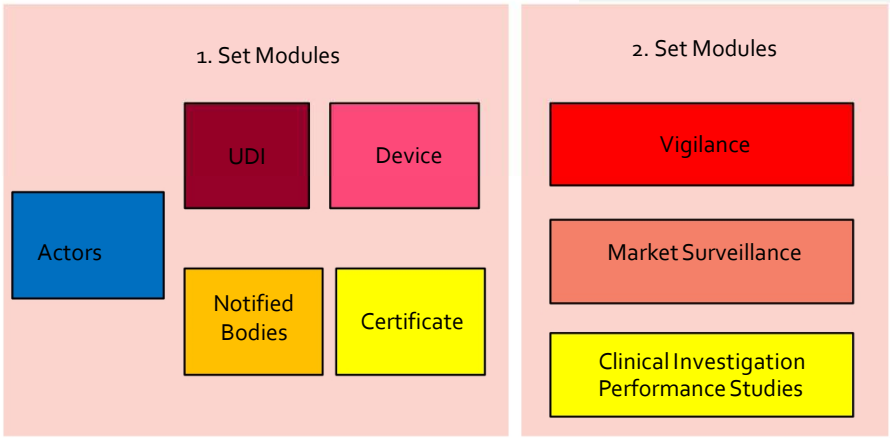
Eudamed Modules – Implementation Plan



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Eudamed Implementation Plan

- Release 1: planned 25.3.2020

To deliver what is absolutely necessary from day 1 for Actors, UDI/Products, Notified Bodies and Certificates

- Release 2: 6 months to 1 year after go live of Release 1

completes Release 1 to reach full functionality for regulatory purposes

- Release 3: 6 months to 1 year after go live of Release 2

Contains functionality which was identified as nice to have to improve the usefulness and user experience of the application

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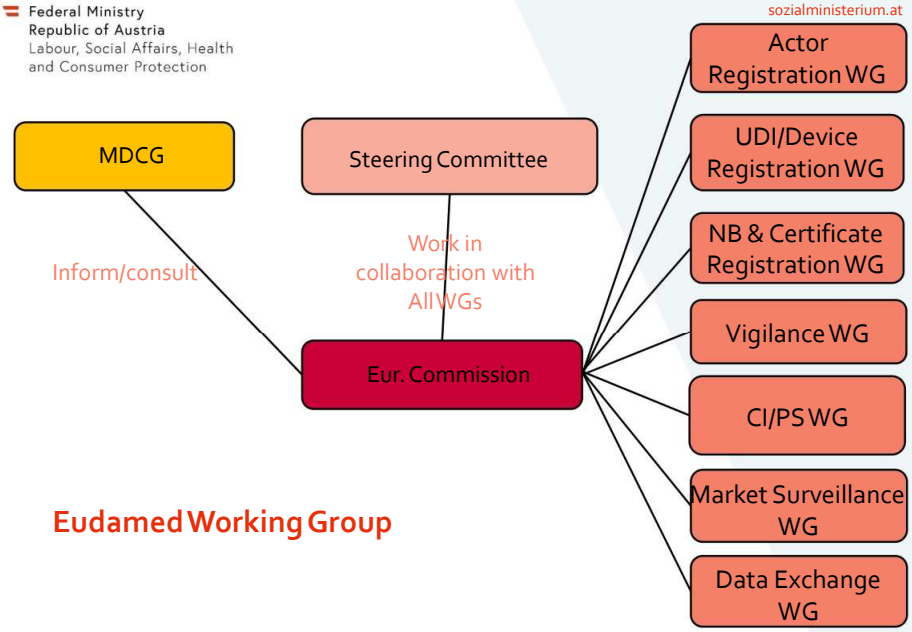

Eudamed Working Group

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Thank you for your attention!

Dr. Martin Renhardt
Federal Ministry for Labour, Social Affairs,
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Strengthened cooperation on Health Technology Assessment in the EU

European Commission
Directorate-General for Health and Food Safety (DG SANTE)
Unit B4 Medical products: quality, safety, innovation
Orsi Nagy

Next Steps I – co-decision procedure the process

- EC adopts a Proposal (January 2018)
- *EP and Council (co-legislators) negotiate (amend/propose changes) – ongoing – EC facilitates and participates in discussions*
- *The institutions agree on a common text*
- *Text is adopted (enter into force and is applied in MS)*

Timelines

Medical Devices regulation

2012 — co-decision procedure

2017 — Entry into Force

2020 — Date of Application MD

2022 — Date of Application IVD

EUnetHTA Joint Action 3

2016 — **2020** — **2021**

End EUnetHTA 3
31/5/2020 + 1 yr extension TBC

HTA proposal

2018 — co-decision procedure

Delayed Application 3 years — Entry into Force

Transition 3 years — Date of Application

Sustainable HTA cooperation All MS — End transition

Timelines not proportionate

MDR / IVDR - IMPLEMENTATION ROLLING PLAN

This Rolling Plan contains the list of identified essential implementing acts, actions and guidance to be put in place by the Commission and/or the MDCG during the transitional period together with relevant information on expected timelines and state-of-play. The information is organised into two main sections (implementing acts; other actions/initiatives). The document will be subject to quarterly review in order to provide the authorities and stakeholders with the most updated information. This document shall be read in conjunction with the "MDR/IVDR roadmap", produced by the Competent Authorities for Medical Devices project (CAMD) in cooperation with the Commission (and available at https://www.camd-europe.eu/regulatory/medical-devices-regulation-vitro-diagnostics-regulation-mdr-ivdr-roadmap), which contains a much more comprehensive overview of all the initiatives (including guidance) expected to be undertaken during the transitional period by the Commission and the National Competent Authorities

Latest update: April 2019

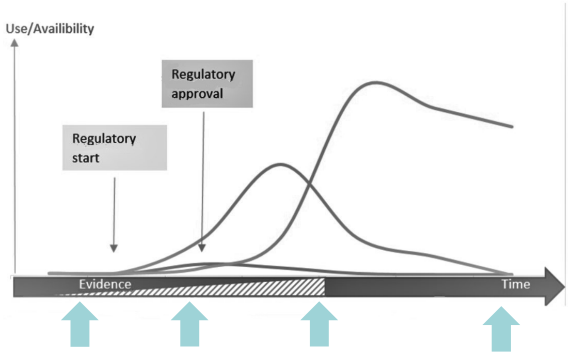
No.	Subject	Legal basis	Description	Expected timelines (expected date of final adoption/date of accomplishment)	State-of-play/Next step
			IMPLEMENTING REGULATIONS/ACTS		
1	Notified bodies scope of designation	Article 42(13) MDR Article 38(13) IVDR	Implementing Act Definition of the list of codes and corresponding types of devices for the purpose of specifying the scope of the designation of notified bodies. This action is an essential pre-condition for the launch of the designation procedure for Notified Bodies	26 November 2017 (Legal deadline)	Adopted and published on 2 November 2017 COMPLETED
2	Reprocessing of single-use medical devices	Article 17(5) MDR	Implementing Act Common specifications laying down requirements related to reprocessing of single-use devices concerning: — risk management, including the analysis of the construction and material, related properties of the device (reverse engineering) and procedures to detect changes in the design of the original device as well as of its planned application after reprocessing, — the validation of procedures for the entire process, including cleaning steps, — the product release and performance testing, — the quality management system, — the reporting of incidents involving devices that have been reprocessed, and — the traceability of reprocessed devices.	November 2019 It shall be noted that, in the event that those CS are not adopted by 26 May 2020, reprocessing shall be performed in accordance with any relevant harmonised standards and national provisions	Formal public consultation (Q2 2019)
3	Common specifications for products without a medical purpose	Articles 1(2) and 9(1) MDR	Implementing Act Common specifications (CS) addressing for any of the groups of products listed in Annex XVI of the MDR, at least, application of risk management as set out in Annex I and, where necessary, clinical evaluation regarding safety. Application of MDR to Annex XVI products depends on the adoption of CS.	Q1 2020	The Commission is currently processing all feedback received by stakeholders fror the informal consultation. Discussion with the Membe States will take place early M 2019.

MDR and IVDR implementing measures rolling plan https://ec.europa.eu/docsroom/documents/34941

Key principles of the HTA proposal

- Joint work on scientific, clinical aspects of HTA
- Joint work driven by Member State HTA bodies
- Ensure high quality, timeliness and transparency
- Ensure use of joint work in national HTA processes
- Member States remain responsible for:
  - Drawing conclusions on added value for their health system
  - Taking subsequent decisions on pricing & reimbursement
- Progressive implementation
- Independence from regulatory assessments – create synergies

Life cycle approach



Horizon scanning
- Filtration and identification of technologies of interest

Early dialogues
Manufacturer to seek the advice of HTA authorities and bodies on the data and evidence

Joint Clinical Assessment
Building on expertise in Member States

Potential re-assessment

Adapted from EUnetHTA

State of play on the HTA proposal at the European Parliament

- **Lead committee:** ENVI
- **Rapporteur:**
  Soledad Cabezon Ruiz (S&D, ES, ENVI)
- **Vote:**
  Plenary adopted amendments on 3 October 2018 and referred back to ENVI
- First reading closed on 14 February 2019

HTA proposal at the Council

- **AT Presidency:**
  7 WP meetings – revised presidency text (Articles 1-8)
  EPSCO 7/12 – progress report dopted(AOB) without any comments
- **Dec 2018- 6 Ministers (BU, CZ, D,FR,PL)** sent a letter to Com and MoH of RO and AUT reiterate willingness to continue cooperation BUT stressing voluntary.
- **RO Presidency:**
  8 meetings planned -1 still ahead
  Opinion of the Council's Legal Service on article 7 and 8
- **FI Presidency**
  7 meetings planned

EP amendments I

EP is largely supportive and mainly remaining consistent with the original objectives of the proposal:

- Suggested a dual legal basis (Article 168(4) TFEU and Article 114 TFEU)
- EP maintains the Commission's approach on "use" and non-duplication of Joint Clinical Assessment (Art 8) but opens the possibilities to complement the JCA by the MS
- Adds `details` on COI, transparency, role of the Coordination Group etc.
- Removes harmonisation of national rules and procedures
- Further selection criteria on medical technologies

EP Amendments II
Joint Clinical Assessments: Product scope

Selection permanent

- ***Medical devices classified as class IIb and III*** for which the relevant expert panels have provided a scientific opinion in the framework of the clinical evaluation consultation procedure (Regulation (EU) 2017/745)
- ***In vitro diagnostic medical devices class D*** for which the relevant expert panels have provided their views in the framework of the clinical evaluation consultation procedure (Regulation (EU) 2017/746)

Amendment by European Parliament: *and considered to be a significant innovation and with potential significant impact on public health or health care systems*.

EP Amendments III
Joint Clinical Assessments: Product scope (cont'd)
Criteria for selection

The Coordination Group shall select the medical devices based on the following criteria:

(a) unmet medical needs;

(b) potential impact on patients, public health, or healthcare systems;

(c) significant cross-border dimension;

(d) major Union-wide added value;

(e) the available resources.

Amendment by European Parliament:

(ea) the need for greater clinical evidence;

(eb) at the request of the health technology developer;

Thank you

Contact: SANTE-HTA@ec.europa.eu

Change of Clinical Assessment by Notified Bodies in the light of the new Regulations

Hans-Heiner Junker
Vice President Team-NB
Chairman NB-Med
Vienna, May 28, 2019

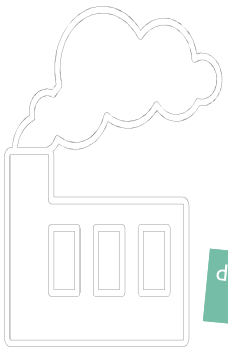
Important changes & improvements*

* Source: http://ec.europa.eu/growth/tools-databases/newsroom

7 Important Modifications

- Stricter pre-market control
- Oversight of notified bodies
- Inclusion of products w/o medical purpose
- EU database
- Implant card
- Rules on clinical data and clinical investigations
- Data about real-life use of devices

Article 10: General obligations of the manufacturer



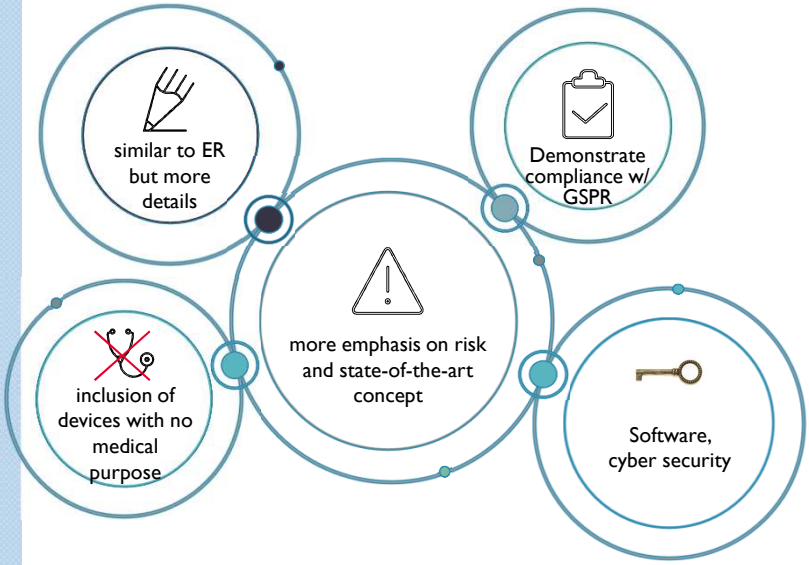
establish, execute, maintain & document a system for **risk management** acc. Section 1a in Annex I

conduct a clinical evaluation, acc. to requirements of Article 61 & Annex XIV, incl. post-market clinical follow-up

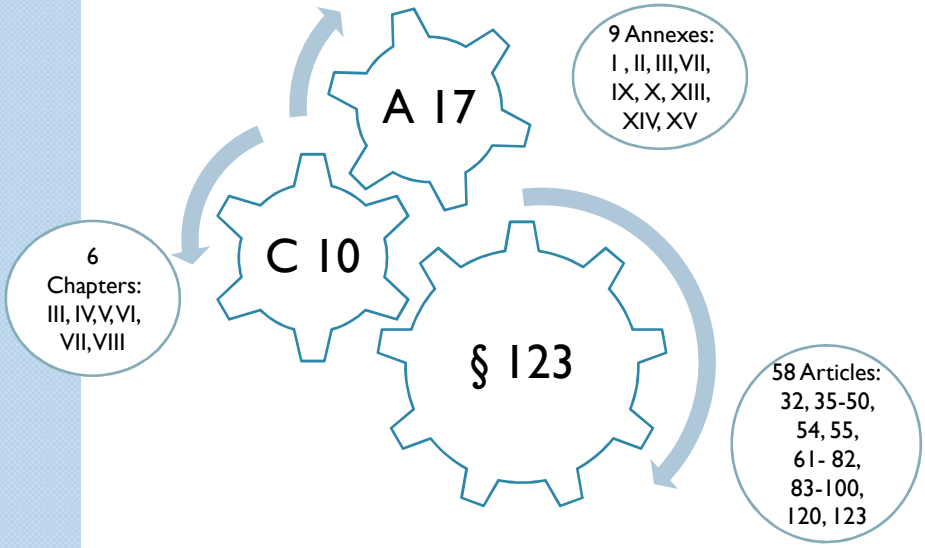
draw up & keep up to date the technical documentation … include the elements of Annex II, etc.

every manufacturer must have a quality system which is in compliance with the MDR, even class I manufacturers

GSPR: New requirements…



MDR: Approx. 50% Clinical Aspects



Article 61: Clinical Evaluation

*"The manufacturer shall specify and justify the **level of clinical evidence** necessary to demonstrate compliance with the relevant **general safety and performance requirements** which shall be appropriate to the characteristics of the device and its intended purpose."*

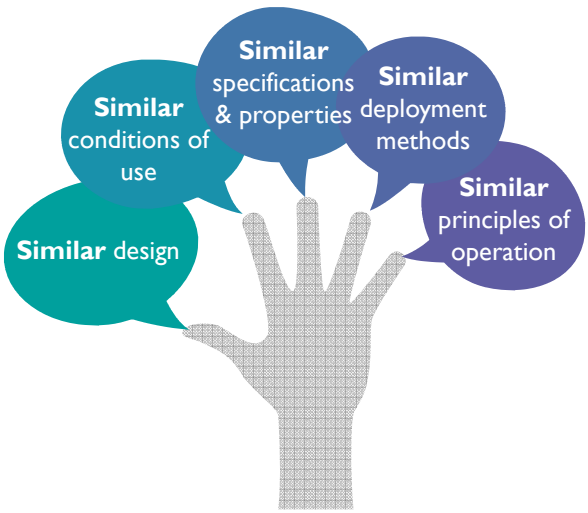
Article 61 and Annex XIV A.3: Equivalence approach

Technical → Biological → Clinical

- These characteristics shall be **similar to such an extent** that there would be **no clinically significant difference in the clinical performance and safety of the device**.
- Based on **proper scientific justification.**
- **Sufficient levels of access** to the data on devices to which Manufacturer is **claiming equivalence**
- **Results in CER , which is part of the TD**

In case no equivalence can be demonstrated clinical investigations need to be performed

Equivalence approach, only possible if technically…



Article 83.1: Post-market surveillance system

For any device, proportionate to the risk class and appropriate for the type of device, manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system which shall be an integral part of the manufacturer's quality management system according to Article 10(9).

Article 83.2 and Annex III: PMS System and plan

Data from PMS System shall in particular be used:

to update

- *the benefit-risk determination and to improve the risk management*
- *the design and manufacturing information, the IFU and the labelling*
- *the clinical evaluation*
- *the summary of safety and clinical performance*

for the identification

- *of needs for preventive, corrective or field safety corrective action*
- *of options to improve the usability, performance and safety*

when relevant,

- *to contribute to the post-market surveillance of other devices*
- *to detect and report trends*

The technical documentation shall be updated accordingly.

Article 84: Post-market surveillance plan

The post-market surveillance system referred to in Article 83 shall be based on a post-market surveillance plan, the requirements for which are set out in Section 1.1 of Annex III.

For devices other than custom-made devices, the post- market surveillance plan shall be part of the technical documentation specified in Annex II.

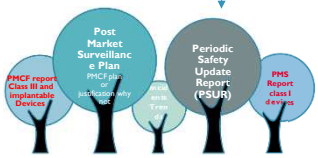
Annex III: Technical Documentation on PMS

Changes compared to MDD & AIMDD

Completely new Annex with new content and requirements to keep PMS-data as part of the Technical Documentation

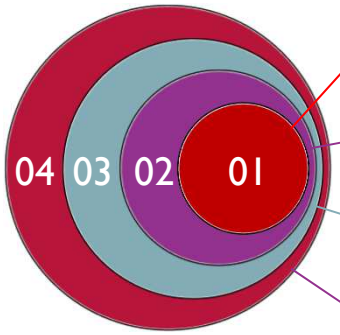
Article 86: Periodic Safety Update Report (PSUR)

Per device and where relevant per category or group of devices, the manufacturer shall prepare a periodic safety update report summarizing the results and conclusions of the analyses of the gathered post-market surveillance data according to Annex III together with a rationale and description of any preventive and corrective actions taken.



Except for class I devices → here: PMS report sufficient

Example: Class III devices, PSUR shall be:



updated annually or when necessary

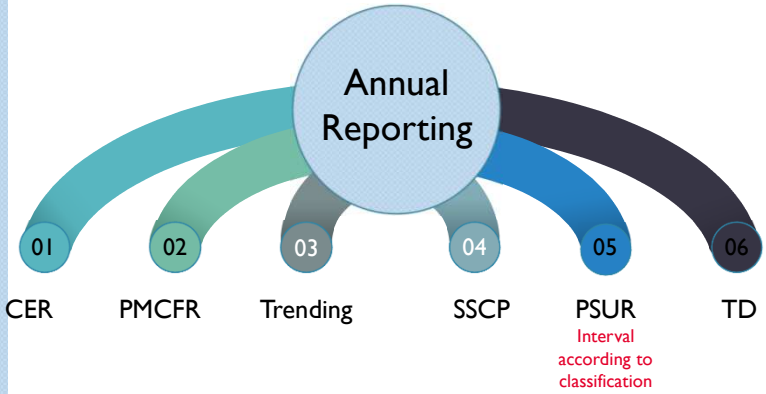
100 % submitted via EUDAMED for assessment by Notified Body annually

submitted in combination with an updated Clinical Evaluation Report

submitted in the language accepted by the Notified Body via Eudamed And NB provides its evaluation as well via Eudamed

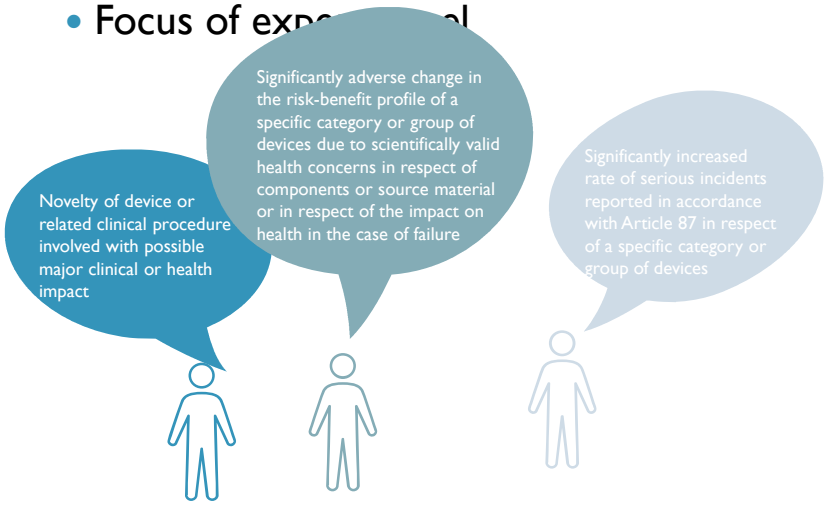
Higher Transparency through Annual Reporting System

Applicable for Class III and Implantable Medical Devices

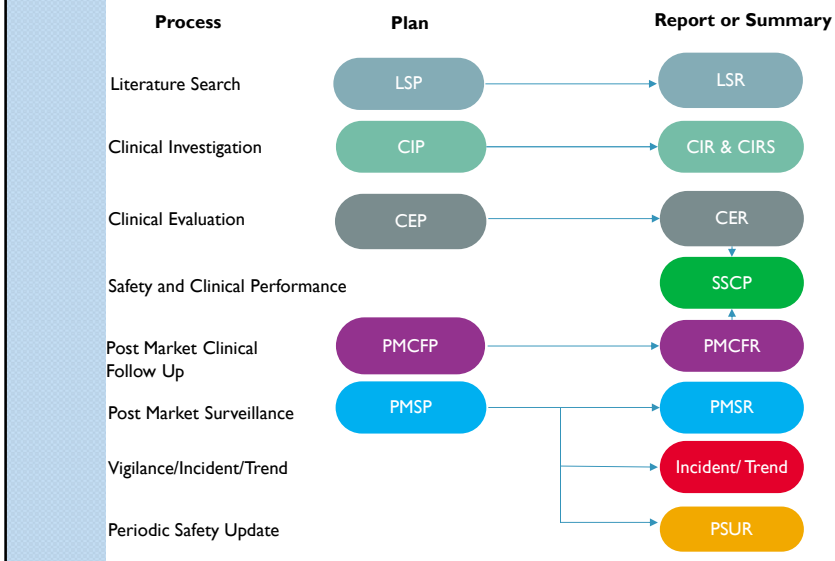


Article 54: Clinical evaluation consultation procedure

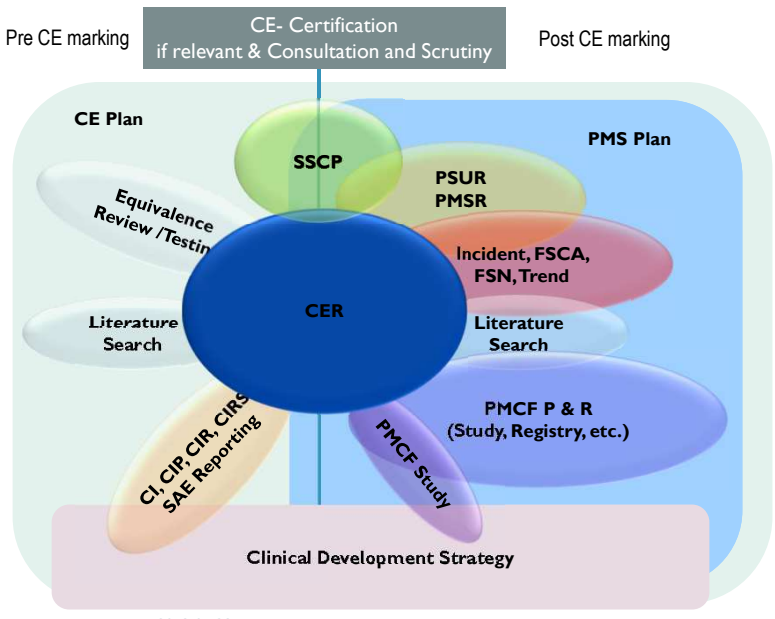
- Focus of exp… …l



Clinical Aspects – Processes, Plans (P), Reports (R), Summary (S)

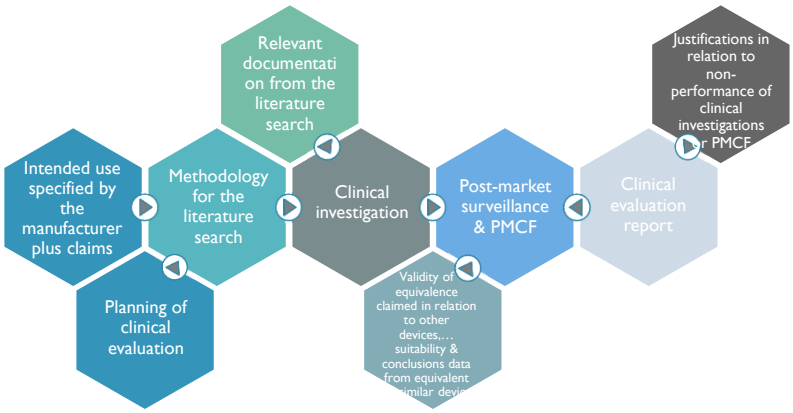


Clinical Approach – A model for processes and documentation



Annex VII 4.5.5: Clinical Evaluation - Duties of the NB

The NBs assessment of clinical evaluations as referred to in Annex XIV shall cover:



Moreover:

- …conclusions from clinical investigations ..valid in the light of the approved clinical investigation plan
- …clinical evaluation adequately addresses the relevant safety and performance requirements provided for in Annex I, that it is appropriately aligned with the risk management requirements, …..that it is appropriately reflected in the information provided relating to the device

Hans-Heiner Junker
Vice President Team-NB
Chairman NB-Med
Vienna, May 28, 2019

Thanks for listening

Change of Clinical Assessment by Notified Bodies in the Light of New Regulations

H.H. Junker, NB-Med chair & F. Schlemmer, Team-NB Director

May 28th 2019 – Vienna

2nd workshop of the EUnetHTA Task Force on HTA and MDR

Team-NB

- **Aims:**
  - Communication with
    - Industry associations
    - European Commission
    - Competent Authorities
  - Promote technical and ethical standards
  - Participate in improving the legal framework
  - Contribute to harmonization
  - Represent Notified Bodies

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New regulations: NB-Med ⇨ NBCG

- **Article 49 - Coordination of notified bodies**
  - Coordination and cooperation between notified bodies
  - shall meet on a regular basis and at least annually

  NBCG is setting up rules and reorganizing following new regulations

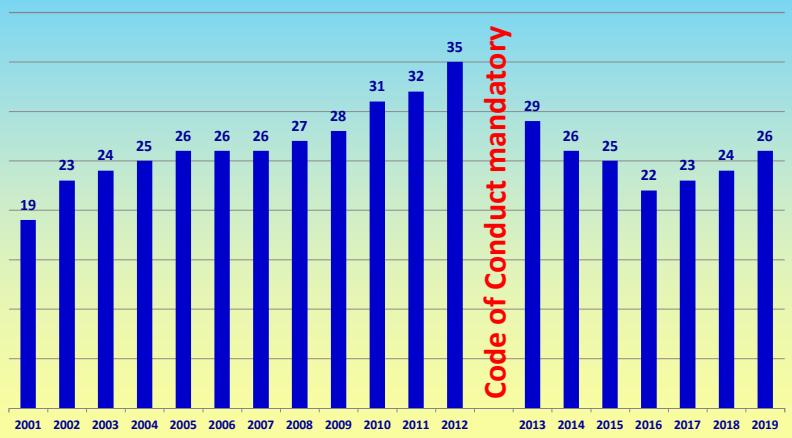
New regulations: NB-Med ⇨ NBCG

- **Aims:**
  - Allows NBs to share experience and exchange views on the application of conformity assessment procedures.
  - Drafts technical recommendations and creates consensus on matters relating to conformity assessment.
  - Advises the Commission, at its request, on medical device legislation.
  - Drafts reports on ethical aspects of the activities of NBs.
  - Ensures consistency with standardisation work at European level.

New regulations: NB-Med ⇨ NBCG

- **NB-Med:**
  - Chair: Hans-Heiner Junker
  - Vice-chair: Suzie Halliday
- **NBRG:**
  - Chair: Nick Baker
  - Vice-chair: Thomas Feldmann

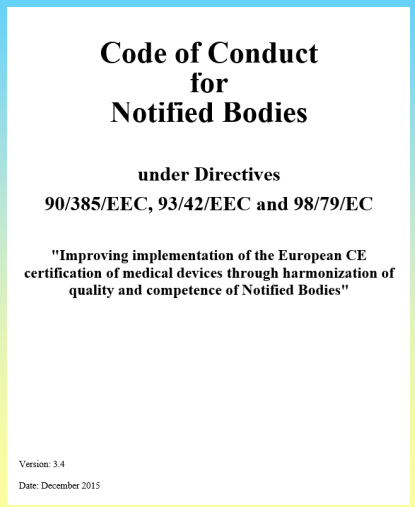
Team-NB : Members



Team-NB : Code of Conduct

- **Mandatory to sign for TEAM-NB members**
- **Version 3.4 approved**

  Available on website
  www.team-nb.org

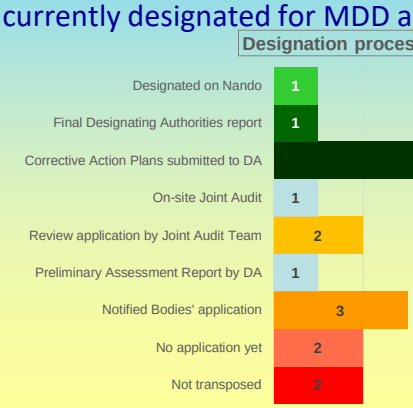


Implementation of the new regulations

- **Team-NB established mirror MDCG working groups from November 2018**
- **Aim: harmonise NBs views and speak as much as possible from 1 voice**
  - prepare the meetings
  - comment the documents
  - set up guidances to harmonise NBs practices, …

MDR Designation process

- **Data collected in December 2018 with responses of 22 out of 24 members** (knowing that 57 Notified Bodies currently designated for MDD and AIMD)



➔ **10 members in the last phases before designation**

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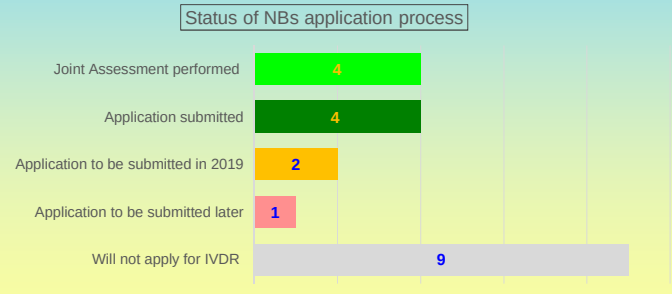
IVDR Designation process

- **Data collected in January 2019 with responses of 20 out of 24 members** (knowing that 10 Notified Bodies members currently designated for IVDD)



➔ **8 members in the designation process**

➔ **3 members intending to apply**

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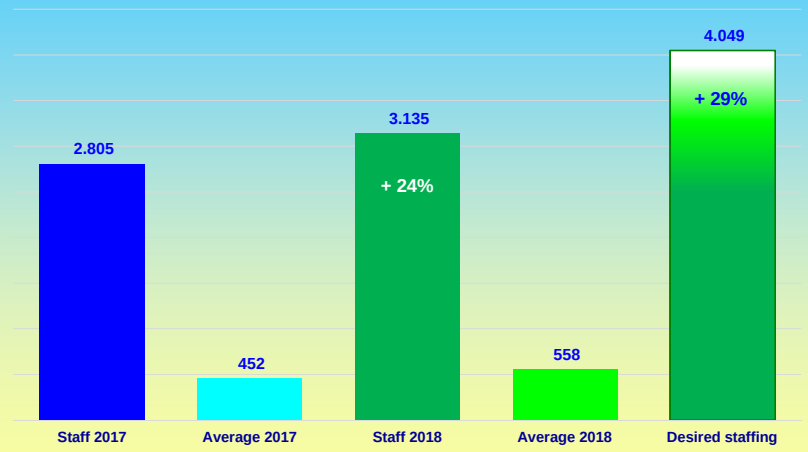
Staff capacities



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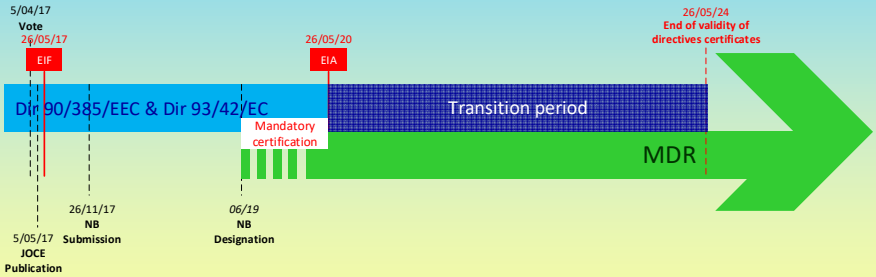
Transition period

- **MDR: From May 26th 2020 to May 2024**
- **IVDR: From May 26th 2022 to May 2024**



- Contract between Manufacturers and NBs
  - update to be signed to allow surveillance audits

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MDR highlights

- **Commission tools**
  - To be adopted by the MDCG
    - Common specifications
    - Delegated and implementing acts
      - **instrument to precise regulation articles**
- **EUDAMED = MD European databank**
  - SRN – single registration number
  - UDI – unique device identifier -> traceability
  - certificates
  - clinical investigations
  - vigilance and market surveillance

Clinical Data

- **Directive 93/42/EEC**
  - Annex X - Clinical evaluation
- **REGULATION (EU) 2017/745**
  - Chapter VI – Clinical evaluation and clinical investigations
  - Annex XIV - Clinical evaluation and post-market clinical follow-up
  - Annex XV - Clinical investigations

Requirements more detailed in new regulation

Contacts : www.team-nb.org

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Hans Heiner Junker	Vice President	(hans-heiner.junker@tuev-sued.de)
Kevin Butcher	Vice President	(kevin.butcher@sgs.com)
Corinne Delorme	Secretary	(corinne.delorme@lne.fr)
Alexey Shiryaev	Treasure	(Alexey.Shiryaev@presafe.com)
Françoise Schlemmer	Director&Secretariat	(schlemmer@quasys.com)

Members :

EUnetHTA-20190528

Session 2: Perspectives of Different Stakeholders on Collaboration Between Medical Device Regulation and HTA. Presentations and Panel Discussion.

Minutes Session 2:

2.1 "Perspective of Medtech Europe" by Yves Verboven. Presentation

2.2 "Perspective of Payers" Statement read by C. Nyst, European Social Insurance Platform (ESIP) as G. Endel was unable to attend.

Notified Bodies check if the device does what it is supposed to do (performance), this is not the same as effectiveness. It would be best if we have best possible evidence already at CE mark stage (including effectiveness). Class IIb and III: clinical evidence should be available for CE mark.
ESIP: working group of medical devices created the statement (that was presented during the Workshop), state of reflection, available to ESIP members.
Social insurance point of view: it is unclear what type of documentation they can have from Notified Bodies. The new regulation states that performance is part of effectiveness, but it is unsure if this will result in better quality studies. Data on patient relevant benefits is needed. If no such data is available, the manufacturer must do a trial and the Notified Body must give them notice that they have to do it.

2.3 "Perspective of Patients" by Valentina Strammiello, European Patient's Forum. Presentation

2.4 "Data to practice, research community perspective" by Piotr Szymanski, European Society of Cardiology. Presentation

Moderated panel discussion (Q& A):
Question to Medtech Europe: Under which preconditions could a collaboration of MDR bodies and HTA contribute to efficient use of resources for industry to provide appropriate data for regulation and reimbursement?
A: We have to ensure that whatever investment we make is responding to questions (safety or effectiveness question) and whatever data is collected, is fit for purpose. We should ensure that there is no duplication. If we evaluate safety, it is a duplication (this is already assessed by MDR). We should make sure that all collected data has a purpose.

Question to patient representative: From a patient perspective, what are the most frustrating parts of the process of making the effective and safe medical devices available to patients? Where would you see the priority areas for improvement of the process?
A: We have a very diverse membership. For patients with the same condition, it is frustrating if not everyone has access to the same products in different countries. What comes before access to healthcare? We need to make sure that patients´ voices are heard, it is meaningful in the process and that they have access to the right technologies. It is not only about having access to the treatment but it is about having access to the right/appropriate treatment.
Q: What are the priority areas for improving access?

A: Early involvement, where unmet need is identified and where quality of life can be improved.

Question to clinician: From the perspective of a clinician, which processes from regulators and HTA bodies can support you in finding the best treatment of individual patients? How could collaboration between these actors support you?
A: Transparency is important and medical societies need to have access to data to be able to analyse the data from CE mark process and to be able to proceed better with guidelines. Physicians have to learn to understand HTA, market access, cost-effectiveness and should be invited to conferences, meetings etc.

Q: It was mentioned that indications for CE marks are often not the same as indications proposed in guidelines, as assessed in HTAs, as reimbursed. What do you propose to do against it i.e. that indications mentioned in CE mark are differing from clinical practice/guidelines (hospital based indications)?
A: As there is no database of CE mark indications, maybe clinical associations should provide this info (CE mark info on indications) as supplement to guidelines.

Q: The indications can differ at hospital level throughout Europe. The question is how to deal with that?
A: Medical societies cannot influence this as it is a political decision. They can just provide information to their members and perhaps as a minimum provide accessible info on marketing information that can be compared with information in the guidelines. Example of bioresorbable stents: there is a general guideline and a physician might not be aware that specific stents might not be appropriate for specific indications.

Q: Patient safety is regulated in MD CE mark regulation: is there a distrust of CE mark regulation?
A: Procedure of safety should be reinforced; there is not a lack of trust, there is a lack of public information around it. We need to advocate better, we need clearer information that is available to the public. We see that the current system does not respond to questions.
A: from the audience: HTA will always assess safety and need data on safety because many more patients are needed to discover rare adverse events (trials only include limited number of patients).
Q: Do you think that the new MDR will change things? Will this speed up access for new technologies in the US? Most of the colleagues do trials in the US.
A: Compared to the US, Europe always has introduced new technologies earlier to the market. We need to keep the innovative advantage but we need the mechanisms to do that. Additional pathways have been implemented to bring innovation in the US.

Q: Real world evidence? Who decides on what measures are to be taken when there are safety reasons? From a patient perspective every single safety issue requires steps to be taken.
A: Post marketing surveillance is done, information is available.
Comment: Even an individual case needs to be further investigated.

Q: Concerns about the EUDAMED database were expressed (will it be publicly available)?

A: There will be no open access to those data. Safety events are reported on a voluntary basis by manufacturers. Vigilance system is set up to provide the information from manufacturer to the European Commission.
A: There is a reporting system which is open to all, not only to manufacturers, but patients and physicians can also report.
A: Market surveillance/user reports can be received from manufacturers, patients and physicians. We are open to reports from all sources. Incident report management: with the new regulation there is a shift to Notified Bodies to report and the Notified Bodies know the device quite well. Clinical experts should be used to make a correct judgement of an incident.

Health Care and access to innovation in Europe — EU Treaty on Functioning of the European Union

1. EU: Article 114.

Harmonizes 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**.

The MDR – IVDR **regulation** (common EU Level) aims to ensure the **smooth functioning of the internal market** , with 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.
MDR-IVDR Regulation sets **high standards of quality and safety for medical devices in order to meet common safety concerns**.

2. Health Care: Article 168

Accords **discretionary powers to Member States pursuant to Article 168(7) TFEU organizing their healthcare systems !**

As regards Article 168(4)(c) TFEU, the MDR-IVDR Regulation sets high standards of quality and safety for medical devices by ensuring, among other things, **that data generated in clinical investigations are reliable and robust** and that the **safety of the subjects participating** in a clinical investigation is **protected**.

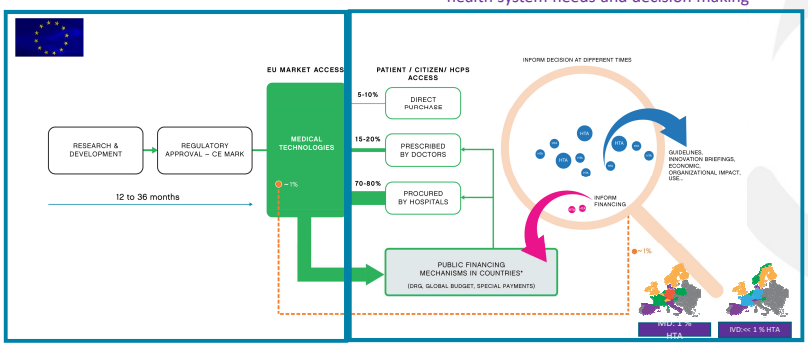
Directive 2011/24/EU - Cross-Border Healthcare Directive :
Including the establishment of an HTA Network (2013) to provide strategic and political guidance to the scientific and technical cooperation at Union-level.

Directive 2014/24/EU - Public Procurement Directive :

Access model of Medical Technologies fosters innovation

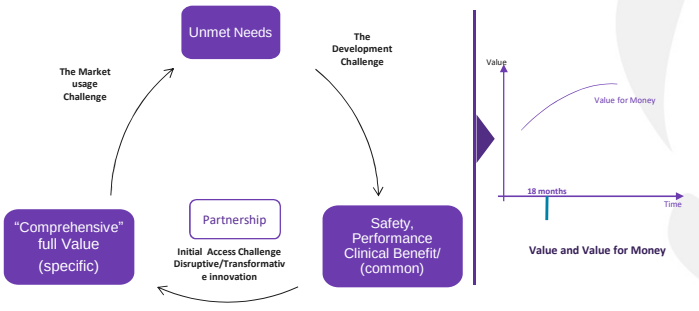
Common EU requirements

Responding to specific decentralized, localized health system needs and decision making



MedTech innovation driven & competitive market dynamics

Future : Value Driven Access Model with progressive adoption of innovation



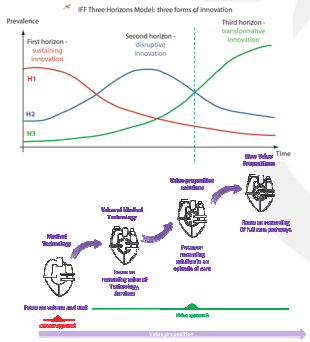
Based upon White Paper Towards Public Private Partnership in EU Healthcare Systems
L. Annemans, M. Callens, D. Commelin et al. Adapted

Specific evidence generation programs for the specific challenges taking the specificities of Medical technologies use in practice into account (learning, continuous innovation, involvement users) and specificities of countries care pathways into account when assessing & rewarding of the value created (complementing the common safety and clinical performance demonstrated as part of CE marking)

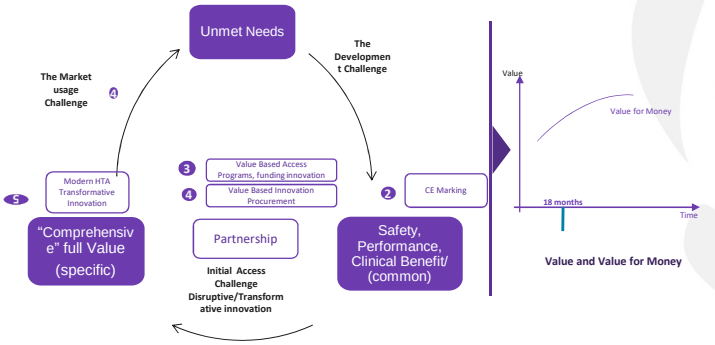
Implementing Value Driven Access

Address specific questions along lifecycle for specific forms of innovation Value Propositions

1. Early Value Assessment
2. MDR, IVDR : Safety & Claimed Clinical Benefit)
3. Value Based Access Programs, for Funding Innovation Real World Evidence
4. Value Based Procurement –" Innovation partnerships" Value based contracting – Real world Evidence
5. Modern Value driven HTA for adoption of transformative Innovation Investment in Innovation – Real world Evidence
6. Deploy Value based (Health - Social Care) funding & Reimbursement Real world Evidence
7. Apply Value of Diagnostic Information (VODI)



Future : Value Driven Access Model with progressive adoption of innovation

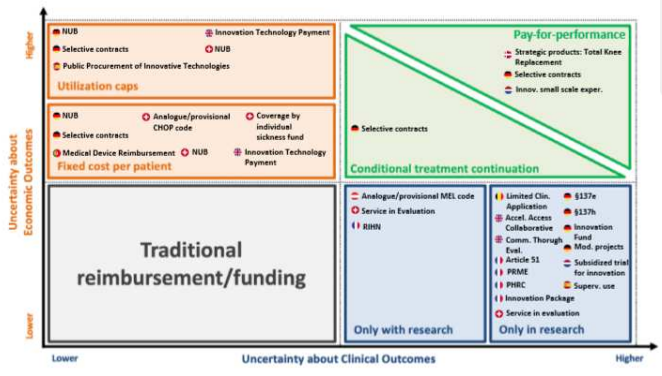


Based upon White Paper Towards Public Private Partnership in EU Healthcare Systems
L. Annemans, M. Callens, D. Commelin et al. Adapted

❷ All Innovations : MDR/IVDR demonstrates safety & clinical benefit

- **Where the 'clinical investigation'** means any systematic investigation involving one or more human subjects, undertaken to **assess** the **safety or performance** of a device;
- Where the '**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;**
- **Where the '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;**

❸ Disruptive innovation: Value based Access Programs can address uncertainties



Transformative Innovations : HTA to inform use and investment/disinvestment

- Medical technologies or solutions that:
  - have the potential to address high unmet patient and/or healthcare needs, of several Member States
  - and require significant structural and/or organizational change
- Adoption will lead to key improvements in patient's and healthcare outcomes, and more sustainable healthcare systems
- a valuable solution to common problems and a strategic investment will be likely taken-up (accelerated adoption) supported by HTA. (possibly collaborative by Member States)

MedTech Europe
from diagnosis to cure

Transformative innovation – HTA for significant structural/organizational change

Modifications in

- clinical pathways

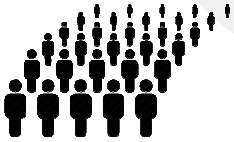
Technologies that allow person-oriented and more efficient approaches for the diagnosis and/or treatment of patients with multiple chronic diseases, situations of frailty and/or of loss of functionalities

- the organisation of healthcare delivery

a Technologies that allow new models of person-centred community-based health delivery.

b.Technologies that allow transfer of skills and tasks from highly trained, high cost personnel to personnel that have less specialised training and are more affordable

overcome challenges regarding accessibility of existing or new transformative innovation of value to patients and health systems .



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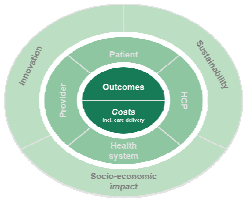
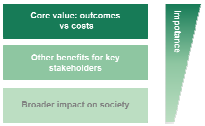
Main Instrument Access - Value Based Procurement





- Innovation Partnerships
- Innovation Procurement
- Procurement of Care / for Care
- Value Based Contracting
- Economic Most Advantageous Solution (MEAT) – Value Based Procurement

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from diagnosis to cure

MDR and HTA separate building blocks of a value based model

Thank you!

Yves Verboven

Director Market Access & Economic Policies
MedTechEurope

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MedTech Europe
from diagnosis to cure

Modern HTA can support the identification and use of transformative innovation

Governance

MS Voluntary cooperation

No to mandatory,
No new legislation

MS driven collaborative groups for joint work with mutual agreed use.

EU Coordination by a specific body within the EU Commission with Medtech knowledge with specific activities.

EU funded

Implementation

Demand driven to inform specific research questions by decision maker's based **on** unmet patients/health system needs

Clear and predictable criteria for the choice of technologies, driven by value not high risk/ cost.

Transformative Innovation Medtech Technologies and solutions

Appropriate timing, for conducting HTA, (not at market entry)

MedTech Europe
from diagnosis to cure

This is a summary of the reflections within the ESIP working group on medical devices, about the MDR and HTA. Therefore, it's NOT a statement.

Intro

The main dimension of the requirements of said MDR still is, unfortunately, safety and performance. Performance means: the manufacturer has to show that the device will really do what it's supposed to do. That's not "effectiveness", which would mean that the device will more than marginally improve patient-relevant outcomes, such as prolonged survival, improved health, improved quality of life.

From a social insurer's point of view, it is unclear what type of documentation we can expect from the notified bodies (Compare EPAR for pharmaceuticals from EMA). The new regulation states that effectiveness should be part of performance measurement. At this implementation stage it is still unclear whether the new regulation will lead to better study results.

The best would be to have the best clinical evidence at the CE marking, including effectiveness data.

In the absence of better study results, post market studies could help and EunetHTA could be of great value. As the manufacturer would anticipate an EU wide assessment of his product, he might improve the quality of market access studies.

1- **Who needs to be involved?**
   Expert panels and representatives of the decision-making bodies of the different health- or social insurance systems, as well as clinical experts;
   Current authorities responsible for market surveillance.

2- **Stage: time of CE marking / time for an HTA evaluation**
   For high risk medical devices (class IIb and III, IVD: C and D), comparative and meaningful clinical evidence should be available at the time for market approval (CE marking) and necessary for reimbursement decisions.

3- **What data do we need?**
   Data on patient-relevant benefit especially for new high-risk devices.
   Those data must reflect the PICO (Patient - Intervention – Comparison - Outcome) scheme (what kind of patients, what indications? Which intervention, what circumstances, what kind of mandatory specialist training etc.? Which treatment will be replaced (control)? What outcomes?).

   If patient-relevant data (at least for the treatment approach as such, if not for the specific product) are not available at the time of market access, it must be mandatory for manufacturers to setup and conduct a trial to provide the missing data. These obligations should be communicated or mandated directly by the responsible notified bodies when setting up the Post-Market Clinical Follow-up (PMCF), and should be part of any consultation of manufacturers, regardless whether this consultation is done by EUnetHTA or another body.

4- **How?**
   In the consultation process, EUnetHTA could recommend requirements (e.g. the PICO scheme) for quality multicentre trials to assess the effectiveness of innovative high-risk devices within existing Coverage with evidence development programs. The mandatory precondition should be that first results of the CE clinical trials indicate that the intervention might have a relevant benefit for the patients, and that a comparative pivotal trial is warranted.

THE EUROPEAN PATIENTS' FORUM

2nd Workshop Patient Involvement in HTA
Valentina Strammiello

28 May 2019

Brussels

@eupatientsforum

"A STRONG PATIENTS' VOICE TO DRIVE BETTER HEALTH IN EUROPE"

"A STRONG PATIENTS' VOICE TO DRIVE BETTER HEALTH IN EUROPE"

EPF European Patients Forum

EPF European Patients Forum

EPF European Patients Forum

"First we're going to run some tests to help pay off the machine."

"A STRONG PATIENTS' VOICE TO DRIVE BETTER HEALTH IN EUROPE"

Patient Perspective

- **Safer medical devices:** high level of patient safety and quality of care throughout the lifecycle of the device
- **Improving transparency and information to patients:** to empower patients and ensure public trust and confidence in the safety of medical devices
- **Patient involvement:** Individually and collectively, in the development process of medical devices and direct involvement of patients in key decision making bodies and scientific committees
- **Equitable access according to patients' needs**

"Seeing patient safety being in the centre of two major European pieces of legislation is a great achievement for us at EPF." Nicola Bedlington, Past EPF Secretary General

MDR and IVDR

Where in the process of MedTech development patient input should be gathered?

Three stages:

1. Clinical investigation /Test
2. Conformity assessment (safety and performance)
3. Surveillance (post market vigilance)

All the information collected at these three stages would be equally valuable in the context of HTA

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About Transparency

Some considerations

1. Increased transparency (Eudamed database),
2. Public summary of safety of high-risk class III devices and implantables,
3. Reinforced post market surveillance and data collection

BUT

1. Concerns about transparency due to limited public access to information
2. No public access to clinical evaluation assessment reports

Patients' privacy concerns

- Fear of discrimination on the grounds of health/genetics: **in the field of employment, insurances -** The consequences of data falling into the wrong hands could threaten livelihoods, confidence, dignity and relationships. Importance of informed consent and anonymised data.
- **Ownership** of data e.g. clinical trials – Who's data is it?
- Concerned of **security mechanisms** (links to interoperability of systems and software) that will be put in place to ensure safe sharing
- Concern for **respect of the law** and **professional secrecy**
- Patients' fundamental right to protection of their data is vital in diverse contexts: healthcare, eHealth, cross-border care, clinical trials,…

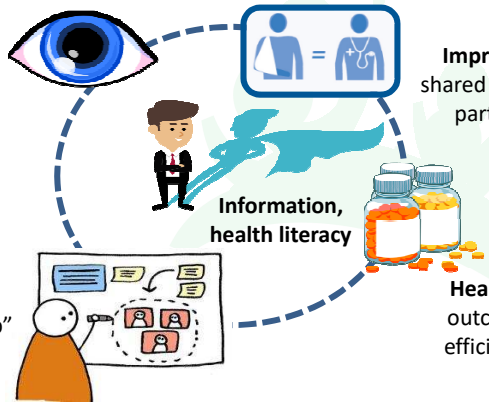
➢ New technologies offer opportunities to collect, use and share health data more efficiently

… but set new challenges for privacy and data security

“ A STRONG PATIENTS' VOICE TO DRIVE BETTER HEALTH IN EUROPE ”

Value of health data vs Transparency of data

Empowerment – having own data, self-management, quality of life



Improving quality – shared decision-making, participative care process

Information, health literacy

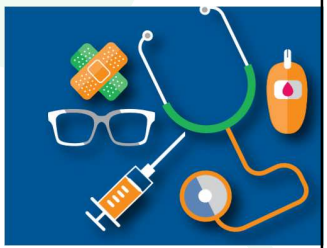
Integrated systems – Person-centred, well coordinated, "joined up" care

Health systems – health outcomes, effectiveness, efficiency in resource use

EPF Position on the EC Proposal for a Regulation on HTA

Medical Devices

- Keeping MDs "in" the regulation
  - to reduce the fragmentation of the MDs market
  - facilitate accessibility to the best (**safer,** more **efficient** etc) technologies to the benefit of patients
- Focus on
  - unmet medical needs,
  - potential impact on patients,
  - public health,
  - healthcare systems significant cross-border dimension,
  - EU-wide added value,
  - available resources



"unmet medical need" and "impact on patients" must be developed with the involvement of patients and patient organisations

- Specific approach to HTA for MDs

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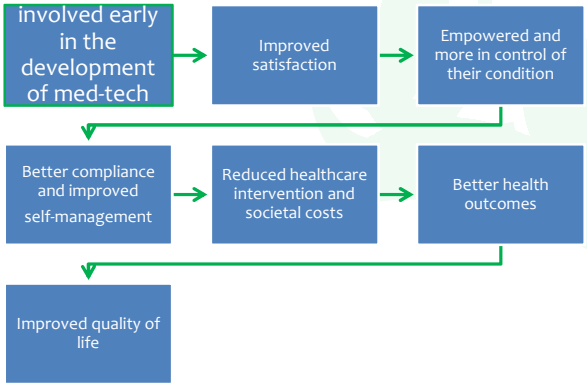
EPF Position on the EC Proposal for a Regulation on HTA

JOINT WORK on HTA

- Joint Scientific Consultation

- **JSC** in line with EPF recommendation that patients and all relevant stakeholders should be consulted with at an early stage of the process
- **Early dialogues** can help in making research and development more focused on patients needs and more predictable for industry
- Clear distinction between EMA scientific advice and clinical assessment
- Strong coordination of JSC and SA
- Potential reduced rudandancies in data collection

The benefits of patient involvement in ED



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Patient Involvement in HTA for MEDTECH

Barriers to patient involvement

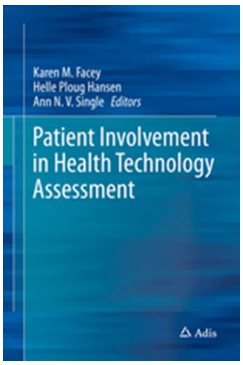
- Heterogeneity and scarcity of HTA processes that include patients' perspectives
- Organisational change needed to facilitate patient involvement
- How to ensure individual/disease specific patient representation
- Difficulties in locating and engaging representative users
- Acceptance of care givers or family members' evidence as proxy for patients' evidence
- Legal concerns

Challenges

1. **Gathering quality data to inform decision making**
2. **Facilitation of patient involvement in early dialogues of medical devices**

"A STRONG PATIENTS' VOICE TO DRIVE BETTER HEALTH IN EUROPE"

Thank you



"If you're not involving patients, you're not doing HTA!"

Dr. Brian O'Rourke, President and CEO of CADTH, Chair of INAHTA

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THANK YOU FOR YOUR ATTENTION!

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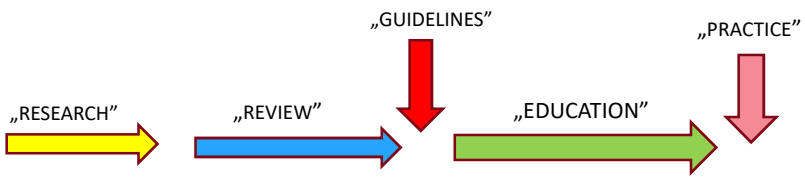
ESC European Society of Cardiology

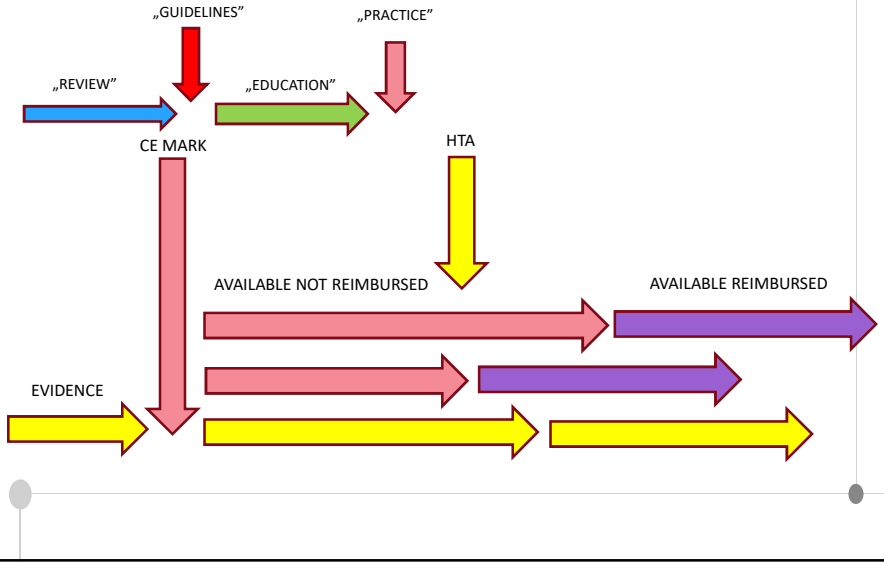
Research community perspective – data to practice

Research community perspective – data to practice

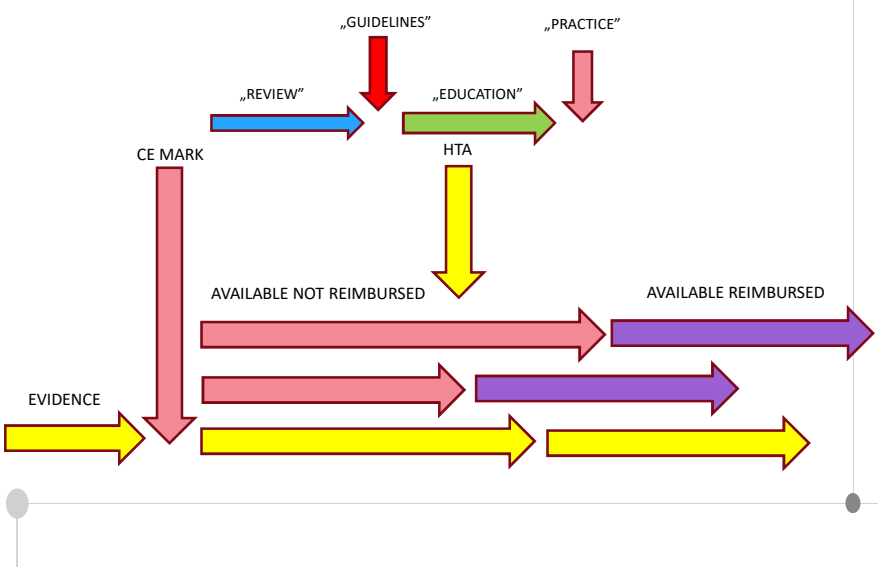
ESC European Society of Cardiology



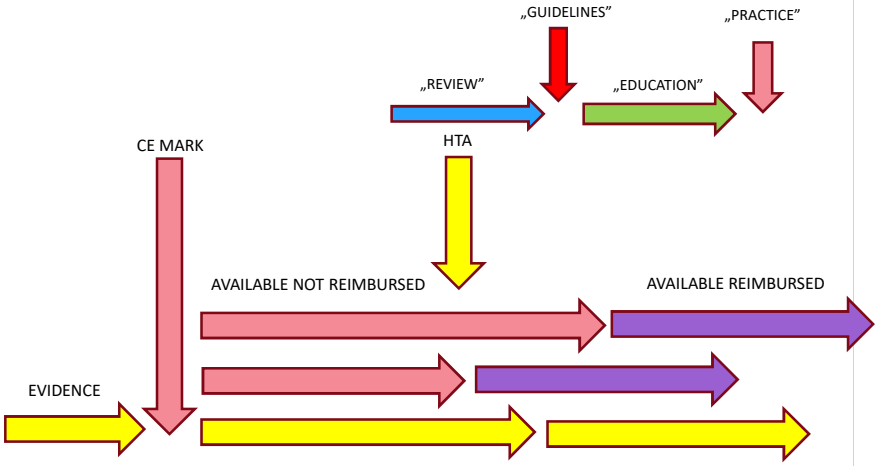
Access to medical technologies



Access to medical technologies



Access to medical technologies



Physicians (providers) and patients perspective – a puzzle…

Access to technologies

CE MARK	COMMERCIALLY AVAILABLE	RECOMMENDED BY THE GUIDELINES	RECOMMENDED BY HTA	LOCALLY AVAILABLE
+	+	-	-	-
+	+	+	-	-
+	+	+	+	-
+	+	+	+	+
+	+	-	+	+
+	-	+	-	-
+	+	-	-	+

Access to technologies

CE MARK	COMMERCIALLY AVAILABLE	RECOMMENDED BY THE GUIDELINES	RECOMMENDED BY HTA	LOCALLY AVAILABLE
+	+	-	-	-
+	+	+	-	-
+	+	+	+	-
+	+	+	+	+
+	+	-	+	+
+	-	+	-	-
+	+	-	-	+

Access to technologies

CE MARK	COMMERCIALLY AVAILABLE	RECOMMENDED BY THE GUIDELINES	RECOMMENDED BY HTA	LOCALLY AVAILABLE
+	+	-	-	-
+	+	+	-	-
+	+	+	+	-
+	+	+	+	+
+	+	-	+	+
+	-	+	-	-
+	+	-	-	+

Access to technologies

CE MARK	COMMERCIALLY AVAILABLE	RECOMMENDED BY THE GUIDELINES	RECOMMENDED BY HTA	LOCALLY AVAILABLE
+	+	-	-	-
+	+	+	-	-
+	+	+	+	-
+	+	+	+	+
+	+	-	+	+
+	-	+	-	-
+	+	-	-	+

A puzzle - indications

Indications according to:	CE mark ≠	the guidelines ≠	financing institution ≠	hospital management

There is a reason to be involved and make the elements of the system

more synchronized

Session 3: Appropriate Evidence for Regulation and HTA by Early Scientific Advice. Presentations and Moderated Discussion

Minutes Session 3:

3.1 "Experience with Early Dialogues on National" by Level Matthias Perleth, Head of Medical Consultancy Department, Joint Federal Committee, Germany

3.2 "Experience of EUnetHTA with Early Dialogues for Medical Devices" by Chantal Guilhaume, Scientific Project Manager Medical, Economic and Public Health Assessment Department, Haute Authorité de Santé

3.3 "Experience of Manufacturers with Early Dialogues" by Pascale Brasseur, Health Economics and Reimbursement Director Spine & Biologics, Medtronic – apologized

Addition/clarifications of the presentation; Q & A
Q: We heard that the number of (Early Dialogue) EDs is not too high in Germany and companies often just ignore the law. The law requires that hospitals submit a dossier but if not, are there any consequences for them? How are the devices paid for?
A: In Germany it is the decision of a hospital to reimburse a device or not. The problem is if the price is higher than the current DRG. The hospital can decide if they reimburse it from other resources or not procure it.

Q: What is your perspective on the added value of ED for MDs?
A: From a national perspective it is easier for a company to receive reimbursement for their product. At the European level there is the possibility to reach a common understanding e.g. on how the studies should be designed. From their experience, pharma manufacturers do request both national and European scientific advice.
A: EDs also help in the scoping of future assessments, ensure to get the outcomes right. For industry it is helpful to think about the added value of their technology and anticipate better what kind of evidence will be needed. In EUnetHTA the objective is to discuss the evidence needed in the full life cycle of the technology. REQueST® tool was designed for that and is now available for public consultation https://www.eunethta.eu/request-tool-and-its-vision-paper-are-now-available-for-public-consultation/
A: It is not clear from the industry proposition what is the added value. It represents a direct link to get the information about different entries in different systems. The investment to prepare a submission on the European level is huge. There is a mismatch in the required effort and the benefit for industry. The opportunity to meet up and be in dialogue with agencies is beneficial. The industry is missing the involvement of those who will use the assessment for decision-making.

Q: How many countries have a national ED process?
A: Not many, especially not for MD. For MD it is often regional agencies. 7 countries are represented in EUnetHTA in EDs (8 partners).
A: Whether it is at national or EU level, it is resource intensive to prepare for advice and the EUnetHTA briefing book is very important. Preparation work of a manufacturer is a value in itself. We cannot give any legally binding advice.

A: There might be different indications depending on the CE mark. You should have only one indication in the end, a lot of time is dedicated by an HTA body, to come up with a common advice.
A: Predictability is increased, when patient representatives are involved, there is a higher chance that unmet need is met. Logistical issues need to be solved, like how to find appropriate patients. We see the potential. Confidentiality of the dossier is an issue.

Take home message: performance is not the same as clinical benefit. We need to recognise differences in the terminology. HTA is not just about cost-effectiveness, it is about whether it is worth the risk.
Comment: If we do not agree that the new regulation includes a clinical benefit under the definition, then we have to start to discuss the definitions, to make sure that we are indeed talking about the same thing and the same applies for quality of life (this might be different from a clinical perspective and from a patient perspective).

Gemeinsamer Bundesausschuss

Session 3: Appropriate Evidence for Regulation and HTA by Early Scientific Advice

Experience with Early Dialogues on National Level

Vienna, May 28, 2019

Matthias Perleth, Rebecca Muckelbauer

Federal Joint Committee, Berlin, Germany

Background: German Federal Joint Committee (G-BA)

- **The G-BA is …**

  the main decision-making body in German health care
  - **statutory health insurance only**

  mandated by law (Social Code Book V) to issue legally binding directives that regulate the benefit package

  comprised of **physicians**, **hospitals**, **sickness funds** and (non-voting) **patient representatives** and three **impartial members** (one chair)
  - **legal supervision by MoH**

Background: Responsibilities of the G-BA

- **Directives to define the benefit package for diagnostic and therapeutic procedures (with or without medical devices) in**
  - Ambulatory Care
  - Hospital Care
  - Dental Care
  - Psychotherapy

  other directives are related to
  - Quality Assurance
  - Pharmaceuticals, vaccinations
  - Planning of numbers and density of doctors in out-patient care
  - disease management programmes

Regulatory and scientific advice

- **Advice by G-BA comprises:**
  - questions related to the process of benefit assessment by G-BA
  - questions regarding prerequisites of coverage
  - questions regarding testing of new device-related methods according to §137e SGB V (“manufacturer application”)
  - questions regarding benefit assessment according to §137h SGB V (new high-risk procedure in hospitals)
  - not legally binding
  - fee depends on the content and extent of advice (up to 10,000€)

Context of benefit assessment of diagnostic and therapeutic procedures

benefit assessment following application by G-BA stakeholder	benefit assessment following application by manufacturer	benefit assessment of high-risk medical device-related methods
• early detection of disease (§25 SGB V) • outpatient care (§135 SGB V) • hospital care (§137c SGB V)	• application by manufacturer of decisive device according to §137e SGB V • application by other commercial company (if no device involved) possible	• includes class IIb and III device-related procedures • newly introduced in hospital care, but not yet reimbursed because too expensive for existing DRG • new theoretical-scientific concept • "particularly invasive"

Numbers

Scientific advice to manufacturers of medical devices

2013	2014	2015	2016	2017	2018	2019*
11	7	8	13	4	8	4

Scientific advice to hospital-related high-risk procedures

2016	2017	2018	2019*
10	4	4	0

Scientific advice to manufacturers of drugs (without administrative requests)

2011	2012	2013	2014	2015	2016	2017	2018	2019*
37	56	94	111	143	137	199	169	83

* as of May 2019

Experiences

- **frequent scientific advice issues:**
  - eligibility of procedure for G-BA assessment
    - e.g. newness, “method” (e.g. injections)
  - design of a trial
  - definition of PICO of a possible trial based on preliminary data
    - most often appropriate comparator, sample size, relevant endpoints
  - position of G-BA regarding already existing or planned trials
  - how to get reimbursement of an innovative technology

- **critical issues:**
  - because of conflicting views of stakeholders G-BA sometimes offers only generic or non-specific answers which is not helpful to companies

Thank you!

Medical devices and diagnostic / treatment methods

- **a diagnostic or therapeutic method is generally defined as**

  a medical procedure embedded in a treatment plan under a physician's care,

  based on a specific theoretical and scientific concept,

  involving medical devices or not,

  involving several steps usually involving medical devices differentiating it from other (one-step) procedures.

Experience of EUnetHTA with Early Dialogues for Medical Devices (EDMD)

Chantal Guilhaume,
Scientific Project Manager, EUnetHTA JA3
Medical, Economic and Public Health Assessment Department
Haute Autorité de Santé (HAS)

EUnetHTA Early Dialogues
Objectives and Principles

- The advice given during a EUnetHTA EDMD:
  - Provides consolidated advice including for **both common advice** (where the participating HTABs are in agreement) but also allows room for **individual HTAB positions**;
  - Is **based on the global evidence generation plan submitted by the Applicant** in the EDMD Application and is valid only within this context;
  - Is **non-binding both for HTABs and for Applicants** as recommendations are based on the state of science at the time the advice is given;
  - **Does not predetermine the outcome of the assessment** performed later by the individual HTA agencies on that technology.

Previous experiences of EU Early Dialogue for Medical Devices

- EUnetHTA ED started in 2012 (Joint Action 2)
  - 13 Early Dialogues : 9 pharma, 2 MD
- A dedicated project: Shaping European Early Dialogues (SEED)
  - 11 Early Dialogues: 8 Pharma, 3 MD
- 5 EDMD included
  - 2 implantable medical devices (cardiology),
  - 1 diagnostic test ,
  - 1 MD aiming at enhancing penetration of active products in parts of the body through physical action,
  - 1 MD in diabetes
- Participating agencies:
  - HAS, AETS-ISCIII, NICE, ASSR, AVALIA-T, G-BA/IQWIG, HIQA, KCE

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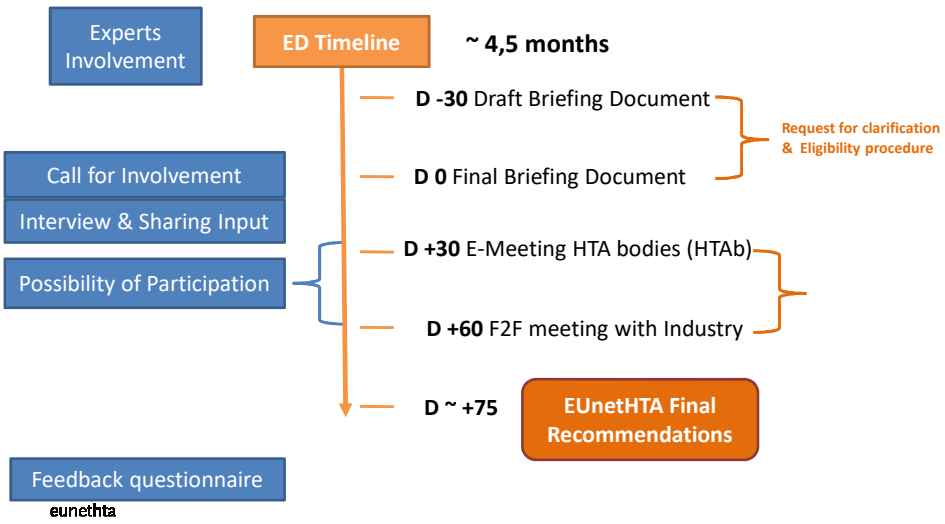
A New EDMD procedure created with Stakeholders



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Experimentation of a 3 pronged approach to expert involvement in ED

Approach	Patient contribution deliverables	HCP contribution deliverables
Approach 1: Individual patient/HCP - interviewed regarding the disease and their experience	• Minutes of the interview • Patient contribution visible in final EUnetHTA recommendations • Feedback questionnaire	• Minutes of the interview • Feedback questionnaire
Approach 2: Approach 1 + discussion with local HTAB regarding submission file (without applicant)	• Minutes of the interview • Patient contribution visible in final EUnetHTA recommendations • Feedback questionnaire	• Minutes of the interview • Feedback questionnaire
Approach 3: Expert; Approach 2 + discussion with all participating HTABs regarding the submission file and participation in the F2F meeting with the applicant	• Minutes of the interview • Share final EUnetHTA recommendations • Feedback questionnaire	• Minutes of the interview • Feedback questionnaire

Specificities of EUnetHTA ED

- **Centralised project management by the EUnetHTA ED Secretariat**

eunethta-has@has-sante.fr

- **Creation of EDMD WP**
  - composed of AVALIA-T (ES), HAS (FR), NICE (UK), and RER (IT).
  - primary responsibilities include:
    - Assessment all Early Dialogue requests for acceptability.
    - Provide feedback to the EUnetHTA ED Secretariat regarding procedural and template revisions.
    - Take turns acting as Scientific Coordinator and Rapporteur for EUnetHTA EDs

- **Priorisation process**

- **Cost currently covered by EUnetHTA or by fees for NICE.**
  - **In the future, new financing system based on fee-for-service approach**

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EUnetHTA Selection Criteria

- EUnetHTA multi-HTA EDMDs are restricted to MDs classified as class IIb and III, in vitro diagnostic, equipment and digital healthcare solutions/connected devices and will be selected for an ED after measurement against the EUnetHTA selection criteria:
  - Unmet medical need;
  - First in class;
  - Potential impact on patients, public health, or healthcare systems.
  - In addition to the above selection criteria, at least 3 HTAB must agree to participate in an ED for the request to be accepted.

EDMD Experience during JA3

- 3 Draft of Briefing books submitted
  - 1 nanotechnology in oncology
  - 1 MD and associated services in metabolic disease
  - 1 MD in cardiology
- Only one ED conducted
  - conducted to test the procedure with the participation of 8 HTAb
  - 4 clinical experts including one during closed HTAb meeting the morning of the F2F
  - no patient expert
- 2 procedure cancelled by the applicant during clarification phase
  - Topics for clarification included:
    - Target population/ positioning
    - Functionality of the MD/procedure required for use
    - Regulatory status
    - Information on previous trials
    - Further detailed on proposed study

All documents available on

https://www.eunethta.eu/services/early-dialogues-for-medical-devices/

- EUnetHTA Multi-HTA Early Dialogues for Medical Devices Guidance Document
- EUnetHTA EDMD Briefing Book Template
- Submission deadlines for EDMD
- EUnetHTA Declaration of Interest and Confidentiality Undertaking (DOICU) Form
- EUnetHTA DOICU handling Procedure Guidelines

Questions about EUnetHTA EDs should be directed to the EUnetHTA ED Secretariat (eunethta-has@has-sante.fr).

Session 4

Session 4.1 What is Appropriate Study Design Along the Life Cycle of Medical Devices? Clinical Investigations of MDs and Trial Designs.

Session 4.2 What is the Appropriate Study Design Along the Life Cycle of Medical Devices Observational Data Presentations and Moderated Discussion

Minutes 4.1 & 4.2:

4.1.1 "The IDEAL-D Concept: Study Designs Along the Life Cycle of Medical Devices" by Bruce Campbell, The IDEAL Group, Past Chair NICE Interventional Procedures and Medical Technologies Advisory Committees
In May 2020 there will be an IDEAL international meeting in Amsterdam.

Comment: We need a global standard on clinical investigations. It was suggested to include IDEAL in the work on developing standards for early feasibility studies. Early feasibility studies might be useful to include IDEAL thoughts into this work.

4.1.2 "RCT Designs Developed Especially for the Challenges of Medical Device Properties. Are they used?" Stefan Sauerland, Head of Department Non-Drug Interventions, IQWiG presented by Petra Schnell-Inderst

4.2.1 "10-Year Experience in Registries and Big Data for Outcome Monitoring of Medical Devices: Implementation of MR/Meddev 2.7.1, rev4 by NBs, PMCF-design: Which Registry for Which Clinical question? Opportunities for Collaboration with HTA by Gerold Labek, Former TÜV SÜD Director Clinical Market Surveillance & Clinical Assessor for Orthopaedic Devices

4.2.2 "Global Cardiac Implant Registries: A Critical Analysis by Peter Kolominsky-Rabas, Director, Interdisciplinary Centre for Health Technology Assessment (HTA) and Public Health, Friedrich-Alexander-University of Erlangen-Nürnberg

4.2.3 "Implementation of MDR/Meddev 2.7.1, rev4 by Industry, ED and PMCF: Opportunities for Collaboration with HTA by Rita Peeters, Sr Director, Regulatory Affairs Policy and Intelligence EMEA, Johnson & Johnson

4.2.4 "State of Implementation Meddev 2.7.1, rev4 & SSCP and Other Guidelines by Tom Melvin, Health Products Regulatory Authority, Ireland Co-chair CIE Working Group

<u>Addition/clarifications of the presentation; panel discussion; Q & A</u>
Q: Regarding real world data, is there any problem with GDPR? Is there an attempt to provide a code of conduct for GDPR?

A: There is a document, which outlines this and which processes have to be available for inspection. It will be difficult to provide data on a patient level; we need aggregated data; anonymised data for data analysis. It is doable and possible.
A: This is going to be a big problem - even before GDPR was in place, I saw a problem with this.

Q: What is behind the certificate? Will this information be made public?
A: Audit reports can be shared between authorities, but are not publicly available. It is visible which product is on the European market, also which Notified Body evaluated it.

A: The summary of safety and clinical performance is a comprehensive document; it contains everything received. The European Commission wants to make this public.

Q: Can you please clarify which parts of the EUDAMED database will be made publicly available? How is it improved?
A: There will be a focus on the clinical part and there is a development team/working group who gathered views on what can be made public. Commercially confidential information would not be made public. Details are still being discussed. We need to get a certain amount of views on this issue soon. A clinical investigation form was developed. Regulators are still discussing this, so no final answers are available yet.

Q: There are different types of post market surveillance, will they be merged? Any trends in that? Or will they stay separate?
A: The industry is looking at alternatives to use real world data in different environments. The current reactive/passive approach is to process data from the registries collecting adverse events/complaints. A more proactive approach would be to formulate hypothesis and to find the data to test it. Who is going to do these studies? Need hospitals to work with our new innovative products. We need to provide data for every product that is currently on the market. We need discussions with the clinical evidence group and talk with Notified Bodies.

Q: Do you foresee patient involvement in the market surveillance? Direct involvement of stakeholders?
A: At an overall work package level there are stakeholder meetings, not sure if a patient representative is there. Due to Brexit, French colleagues are now coordinating this work. There are a couple of different deliverables and the deadline is November this year. Tom Melvin will link Valentina Strammiello with French colleagues.

Q: From your point of view: Could the IDEAL-D concept serve as a basis for guidance on study design along the life cycle of medical devices?
A: yes
A: The requirement is evidence; clinical data are collected by use of the device. The definition is wider (animal tests, etc.), there is more to evidence (patient feedback). What happens if a new risk emerges? From our perspective – how to match this with ideal concept?
A: What is missed is the real question, the question about the device? It might be simpler to have a question for one country, difficult to have one for whole Europe.
A: Need to use a life cycle approach.

Q: Is there any European approach to register data? Do not see a coordinated approach, to ensure quality of registers.
A: Systematic EU approach to access registers and access to stakeholders. Leave it to the market or some regulatory approach? Registries have their own interests (academic, financial etc.) and there is often competition between them (business opportunity for them as they generate income).

A: It is a problem how to use the registries, there is no standard how the use should be reflected. Majority of registries are not published and what they publish is general data, we need a dedicated data analysis on a specific question. You need a special evaluation based on an evaluation plan. This is hardly ever published as an annual report.
A: In the future also the electronic health record should be unified.

A: REQueST® tool. Strongly encourage Notified Bodies to look at this. Really important that it is being used, was produced by WP5 in EUnetHTA JA3.

The IDEAL-D concept: Study designs along the life cycle of medical devices

Bruce Campbell
EUnetHTA - Vienna
28 May 2019

Confessions

- Past Chair NICE Advisory Committees
  - Interventional Procedures (2002-15)
  - Medical Technologies (2009-15)
- Non-Executive Director Medicines and Healthcare products Regulatory Agency (MHRA) (2015-21)
- Vascular Surgeon
- Inaugural member of Balliol/IDEAL group (2007-)
- Advisory member of Council, IDEAL Collaboration

The origins of IDEAL - 1

- Framework for new surgical procedures
- Evidence through iterative phases
- Unlike drugs, “complex interventions”
- Additional complexities for surgery

The origins of IDEAL - 2

UK Medical Research Council recommendations for complex interventions (2000, 2008):

- Development & evaluation - iterative phases
- Experimental not observational designs, when possible
- Measure outcomes as well as process
- Detailed descriptions to improve reproducibility, evidence synthesis and wider implementation

The origins and evolution of IDEAL

- 2007-9 Expert group - Balliol College Oxford International – surgeons, academics, HTA
- 2009 Three Lancet papers: Paper 3: *"No surgical innovation without evaluation: the IDEAL recommendations"*
- Annual meetings; ADOPTION; IDEAL Collaboration
- **Move towards devices** – FDA (2012); MDEpiNet; meetings in New York 2014, Oxford 2016; BMJ 2016

IDEAL: "No surgical innovation without evaluation"

McCulloch, Altman, Campbell et al Lancet 2009; 374: 1105-12

Framework for evidence generation on new procedures

Stage 1: **Idea**

Stage 2a: **Development**

Stage 2b: **Exploration**

Stage 3: **Assessment**

Stage 4: **Long term**

Stage 1 – IDEA: Proof of concept

- **Patients:** "First in human" (…. <10)
- **Operators:** Very few, innovators
- **Output:** Description (functionally useful)
- **Intervention:** Inception, evolution

- **Method:** Structured case reports
  ? Register ?
- **Outcomes:** Proof of concept, technical achievement, disasters, dramatic successes

Stage 2a – Development
Safety, efficacy

- **Patients:** Few, selected (10s)
- **Operators:** Few innovators, early adopters
- **Intervention:** Evolving, iterative improvements

- **Method:** Prospective development (cohort) studies; reporting and explaining modifications
- **Outcomes:** Mainly safety; technical and procedural success

Stage 2b – Exploration

Efficacy : Feasibility of definitive RCT

- **Patients:** Many, wider indications (100s)
- **Operators:** More - early majority
- **Intervention:** Procedure refinement; learning curves; indications; quality control

- **Method:** Research database; learning curve evaluation; feasibility RCT
- **Outcomes:** Efficacy and safety. Clinical; short-term; patient centred; feasibility outcomes

Stage 3 – Assessment

Comparative effectiveness

- **Patients:** Many, defined wider indications (100s +)
- **Operators:** Many
- **Intervention:** Stable

- **Method:** RCT ± modifications, alternative designs
- **Outcomes:** Clinical outcomes – specific & graded; medium & long-term outcomes; patient-centred; ?cost effectiveness?

Stage 4 – Long-term: Surveillance

Long-term effects and outcomes

- **Patients:** All eligible
- **Operators:** All eligible
- **Intervention:** Stable

- **Method:** Register/registry, database, linkage "Real World Evidence",
- **Outcomes:** Long-term outcomes; rare events; indication creep; performance variation; quality assurance

IDEAL for devices – IDEAL-D

Sedrakyan, Campbell, Merino et al. IDEAL-D: a rational framework for evaluating & regulating the use of medical devices. **BMJ 2016**; 353: i2372

- Device issues similar to procedures:
  - User-dependent; learning curves
  - Modifications over time
  - Difficulties blinding in trials …

- Device issues different to procedures which require adaptation of IDEAL ……..

IDEAL-D: modifications for devices

(focus on higher-risk devices, esp. implants)

Need for Stage 0

- **Preclinical studies** - product design and testing
- **Difficulties:**
  - Balance protecting intellectual property vs evidence
  - Difficulties in emulating long-term performance
  - No internationally agreed minimum reporting standards

- **IDEAL proposals for framework under construction**
  - Categorises appropriate studies in 4 domains:
    - Device
    - Operator and Usability
    - Patient
    - Health System
  - Takes account of FDA regulations and EU Devices Regs

IDEAL-D: modifications for devices

Stage 1

- No change but “ideally” mandate reporting
  - Confidential reporting all first-in-human procedures
  - Functionally useful description
  - ? Start register from first use (or existing register)
  - In future: mandate to search register to avoid repeating mistakes

- Difficulties
  - protection from legal challenges if harmful first use
  - possible legal discovery protection as in aviation

IDEAL-D: modifications for devices Stage 2

Combine Stages 2a (Development) & 2b (Exploration)

- Less iterative development than procedures
- Most device iterations occur during Stage 0-1
- Single manufacturer (not consensus of surgeons)

- Prospective exploration studies (*?mandate*)
- Facilitate progression to definitive RCT
  - Incorporate parallel qualitative research
  - Evaluate operator learning curves
  - Pre-specify subgroup analysis of controversial variants in use technique or indications

IDEAL-D: modifications for devices

Stage 3 (Assessment – typically RCT**)**

- Selective judgement on need for RCTs
- ? RCTs of "me too" devices *(Guideline IDEAL position paper in development)*
- Alternative designs - e.g. tracker trials, adaptive designs (for incremental innovations, etc.)

- Economic modelling (controversy within IDEAL)

IDEAL-D: modifications for devices

Stage 4 – Long term: surveillance

- Enhanced by UDIs and related data systems
- ?Start registries earlier (from first clinical use)
  - Potent for safety signals
  - Opportunity for nested RCTs
  - Risk adjustment techniques for small or long-term effects, when many confounders & RCT infeasible
- Subsequent similar devices - comparisons

Some current activities…..

Joint IDEAL/MHRA project:

- Mapping IDEAL onto new MedDev Regulations

- Reporting Guidelines for IDEAL format studies
- Proposals for detailed Framework Stage 0
- Position paper on RCTs for new devices
- Paper on incorporation of RWE into IDEAL Stages

New Journal – BMJ Surgery I&T

- Surgery, interventions and health technologies
- Editors – Peter McCulloch, Art Sedrakyan
- Focus on IDEAL principles

- **IDEAL meeting 2019** – Trinity College Oxford
- **IDEAL International meeting 2020 Amsterdam**

Conclusion: IDEAL-D

- A continuous life-cycle evaluation process
- Graded, responsible accrual of evidence
- Could allow earlier patient access
- “Ideally” international agreements on:
  - Mandatory data collection from earliest stage
  - Cooperative registries

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

RCT designs developed especially for the challenges of medical device properties – are they used?

Stefan Sauerland, MD MPH
Head of Department Non-Drug Interventions

Presented by Petra Schnell-Inderst, LBI HTA, Coordinator of the EUnetHTA Task Force for HTA and MDR

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Where are we?

Research topic	Study design	Research aim
Drug	**RCT (+/- blinding)**	**Effectiveness**
Medical device	Non-RCT (interventional)	Cost-effectiveness
Diagnostic test	Test accuracy	Safety
Non-drug therapy (e.g. surgery)	Case series	Feasibility

Where are the problems?

1. Definition of intervention
2. Device changes over time
3. Difficulty of blinding
4. User dependency
5. Strong user preferences
6. Lack of long-term data

Recommended solutions for:

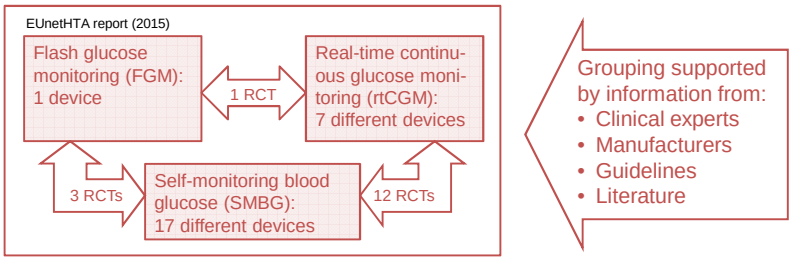
- Trialists and manufacturers
- HTA agencies

https://www.eunethta.eu/wp-content/uploads/2018/01/Therapeutic-medical-devices_Guideline_Final-Nov-2015.pdf

Solving problem #1: Definition of the intervention

- Use a logic model to frame the research question
- Clearly differentiate between single-technology assessment (i.e. one device) and multi-technology assessment

No application found in EUnetHTA reports



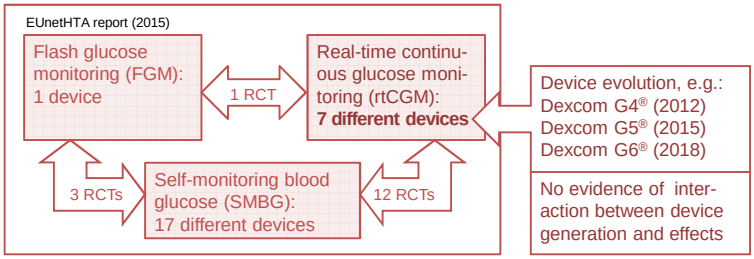
Grouping supported by information from:
- Clinical experts
- Manufacturers
- Guidelines
- Literature

EUnetHTA, 2015: https://www.eunethta.eu/wp-content/uploads/2018/01/Therapeutic-medical-devices_Guideline_Final-Nov-2015.pdf

Solving problem #2: Devices changes over time

- Do tracker trials (flexible RCT protocols allowing for interim analyses)
- Investigate on a within- or between-trial level whether device changes make a difference

No application found (in PubMed search)



Lilford RJ, Braunholtz DA, Greenhalgh R, Edwards SJ. Trials and fast changing technologies: the case for tracker studies. BMJ 2000; 320: 43-6.
EUnetHTA https://www.eunethta.eu/wp-content/uploads/2018/07/OTJA08_CGM-real-time-and-FGM-aspersonal2c-standalone-systems-in-patients-with-diabetes-mellitus-treatedwith-insulin.pdf

Solving problem #3: Difficulty of blinding

- At least perform outcome assessment in a blinded way
- Use objective outcomes (both in RCTs and in HTA)
  - Application in EUnetHTA report on CGM:
    - Focus on HbA1c levels, hypoglycaemia and severe hypoglycaemic events
    - Avoid less valid surrogate endpoints, e.g. time in target glycaemic range

Solving problem #4: User dependency

- Check RCT (or other) data for a possible association between user proficiency and treatment effect
  - Application in EUnetHTA report on CGM:

Author, year, reference	Riveline et.al 2012. Riveline J-P, Schaepelynck P, Chaillous L, et al. Assessment of Patient-Led or Physician-Driven Continuous Glucose Monitoring in Patients With Poorly Controlled Type 1 Diabetes Using Basal-Bolus Insulin Regimens: A 1-year multicenter study. Diabetes Care. 2012; 35(5):965-971. doi:10.2337/dc11-2021.
Training:	In groups 1 and 2, 47.6% of patients had received optimal training. These optimally trained patients exhibited greater improvement in HbA1c than the others. This difference remained significant after adjustment for compliance with CGM use (ΔHbA1c: -0.71 ± 0.81 vs. -0.30 ± 0.81, P = 0.033).

  - Recommendation: Patients “should receive structured education to ensure they can maximise their use and benefit from such technology.”

EUnetHTA https://www.eunethta.eu/wp-content/uploads/2018/07/OTJA08_CGM-real-time-and-FGM-aspersonal2c-standalone-systems-in-patients-with-diabetes-mellitus-treatedwith-insulin.pdf

Solving problem #5: Strong user preferences

- Use cluster-randomized trials
  - Application in medical device research:
    Mainly used in low- and middle-income countries, emergency settings, or for organizational changes.
- Use expertise-based trials
  - “Use […] is growing, but remains uncommon.
  - Benefits … high levels of recruitment and compliance with allocation, value seems context-specific”
- Use Zelen’s design (i.e. consent after randomization)
  - Application in medical research: Only 2 to 3 trials / year

PubMed search (May 24th, 2019): cluster-randomi* AND device* AND Randomized Controlled Trial[ptyp] = 120 hits
Cook JA, et al.: A systematic review of the use of an expertise-based randomised controlled trial design. Trials 2015; 16: 241.
Adamson J, et al.: Review of RCTs using the post-randomised consent (Zelen's) design. Contemp Clin Trials 2006; 27: 305-19.

Solving problem #6: Lack of long-term data

- For the assessment of long-term safety, include
  - disease- or MD-specific registries of high quality and
  - post marketing surveillance data

- Application in EUnetHTA report on CGM:
  - Only short-term data from RCTs available
  - Inclusion of registry or PMS data planned but unsuccessful

- Registries also lack long-term data on CGM ?!

Wong JC, et al.: Real-time continuous glucose monitoring among participants in the T1D Exchange clinic registry. Diabetes Care 2014; 37: 2702-9.

Summary and conclusions

- Specific modifications of the standard RCTs design are rarely used – obviously due to lacking need.
- For the vast majority of medical devices, standard research methodology is applicable and sufficient.
- To some extent, we have to accept that non-drug research is less rigorous as compared to drug studies.

Sauerland S, Fujita-Rohwerder N, Zens Y, Molnar S. Premarket evaluation of medical devices: a cross-sectional analysis of clinical studies submitted to a German ethics committee. BMJ Open 2019; 9(2): e027041. https://www.ncbi.nlm.nih.gov/pubmed/30798319

10-Year Experience in Registries and Big Data for Outcome Monitoring of Medical Devices: Implementation of MR/Meddev 2.7.1, rev4 by NBs, PMCF-design

Ass. Prof. Dr. Gerold Labek
President EARN

What´s the problem – the clinical perspective Oxford Uni

Acta Orthopaedica 2011; 82 (2): 131–135 131

Outcome and reproducibility of data concerning the Oxford unicompartmental knee arthroplasty

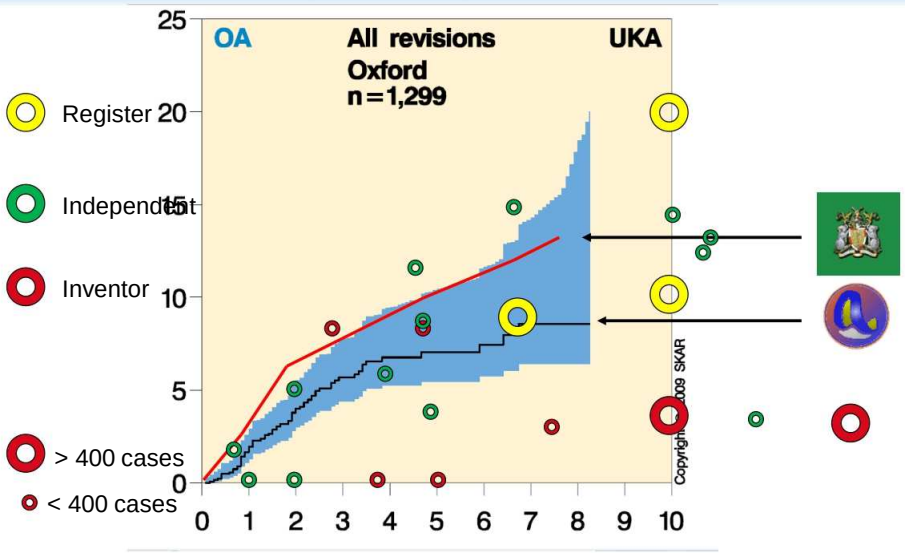
A structured literature review including arthroplasty registry data

Gerold Labek, Kathrin Sekyra, Wolfram Pawelka, Wolfgang Janda, and Bernd Stöckl

Metaanalysis Oxford Uni

- 23 Publications included
- 20 sample based studies
  - 7 by the inventor´s group, Oxford,Nuffield
  - 13 independent publications
- 3 based on National Arthroplasty Register datasets (2x SF, 1x S)
- 3 Annual Reports (S, SF, AUS)

Metaanalysis Oxford Uni



Metaanalysis Oxford Uni

	Number	FUP	Revision Rate [%]	Number primaries	Number Revisions	Observed component years	Revisions per 100 observed component years	CI	Factor Difference to Register
Inventor studies	7	9,64	4,30	1559	67	15029	0,45	0,35-0,57	4,40
Independnt clinical studies	13	4,99	6,09	1445	88	7205	1,22	0,99-1,50	1,61
Total clinical studies	20	7,40	5,16	3004	155	22234	0,70	0,60-0,82	2,82
Register Journal publications	3	9,04	14,51	1951	283	17638	1,60	1,43-1,80	
Registers Annual Reports	3	3,51	6,88	11985	825	42037	1,96	1,83-2,10	

One-third of knee replacement patients are candidates for a mobile bearing UKA, surgeon says

"At least one in three knees that require knee replacement are appropriate for a unicompartmental knee replacement," and would meet all recommended indications and contraindications for it, Murray said at the Knee Society Specialty Day Meeting during the 2010 Annual Meeting of the American Academy of Orthopaedic Surgeons, here.

"Two-thirds of our patients are not ideal and have some of these contraindications, yet there is no difference in the outcome between those who have contraindications and those who do not."

Metaanalysis Oxford Uni

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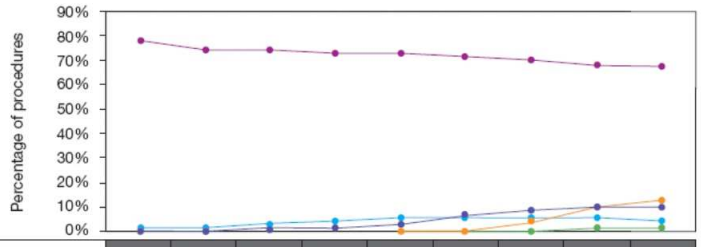
EUROPEAN ARTHROPLASTY REGISTER

Figure 2.25

Top five unicondylar knee brands, trends 2003 to 2011.

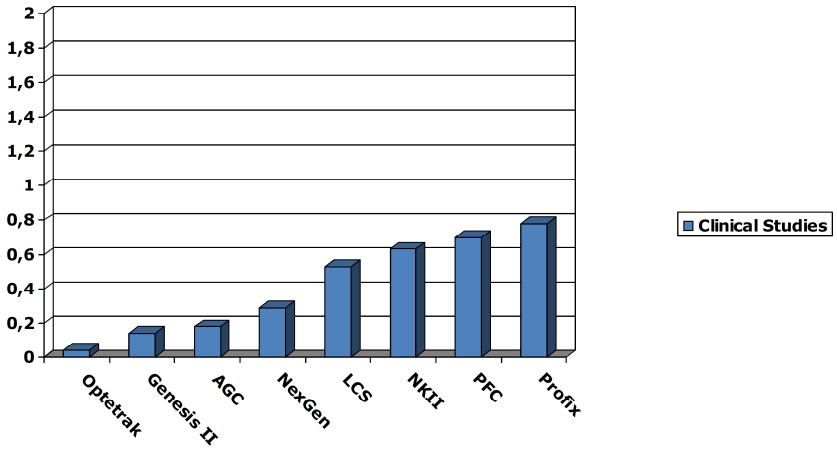


Year	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number of components used	2,226	4,256	5,428	5,740	6,640	7,069	7,146	7,407	6,811

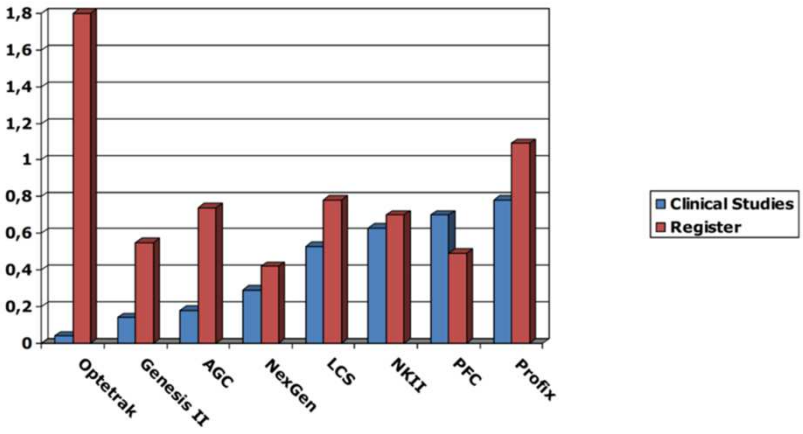
Oxford Partial Knee — AMC/Uniglide — Sigma HP — Triathlon Uni — Zimmer Uni

Impact on daily decisions

EAR NETWORK
EUROPEAN ARTHROPLASTY REGISTER



Impact on daily decisions

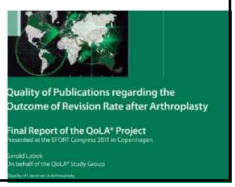


A single observation?

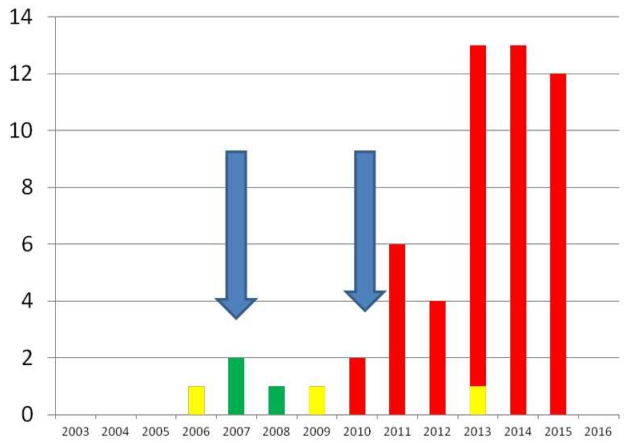
- 1/3 of data to orthopaedic devices not reproducable
- US Publications

- EU-Journals: 7% of cases by Inventor
- US-Journals 55% by Inventor
- 2 Journals identified publishing predominantly „very positive results by implant designers“

- Active implant designers in US supported by manufacturers



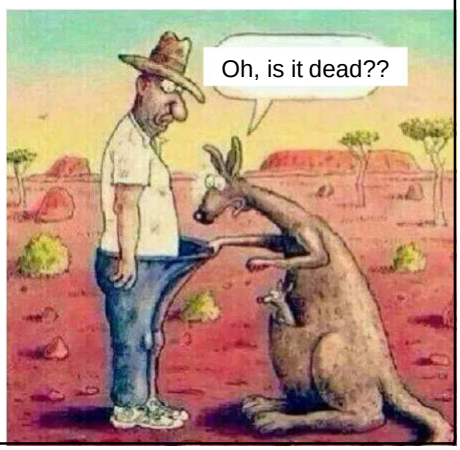
Evidence for ASR/MDD, MEDDEV 2.7.1. rev 3



DePuy ASR Hip Lawsuits
$2.5 Billion Settlement

Conclusions

- Systematic Problems around clinical data by studies as single source
  ➔Wrong Decisions



Reactions by MDR/MEDDEV 2.7/1 rev 4

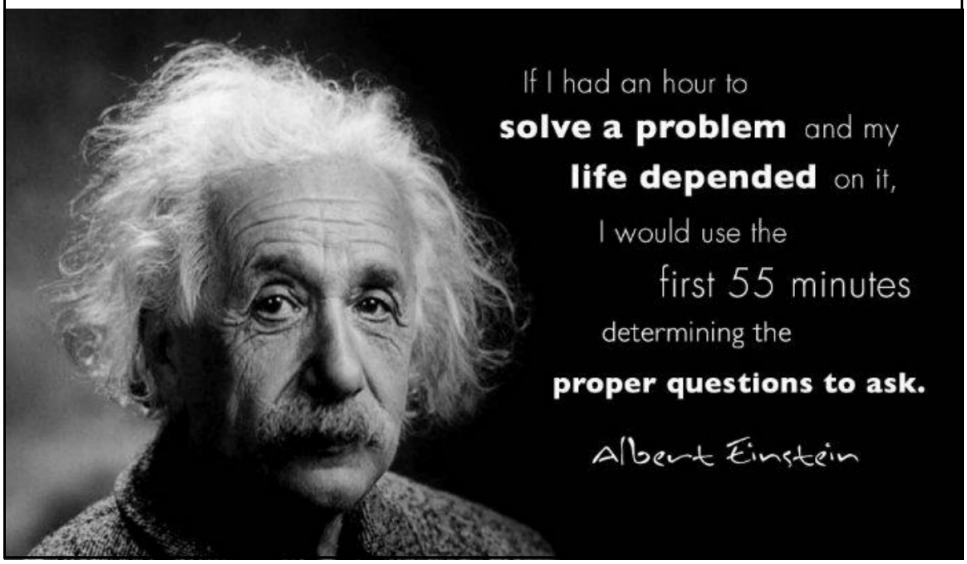
- Clinical Studies (any kind, systematic search strategy)
- Systematic Reviews
  - Cochrane
  - HTA
  - Metaanalyses
  - Guidelines, Consensus Papers

Clinical Studies

- Implant Registry Reports

Market Experience / Real World Evidence

MDR and Registries




EARO
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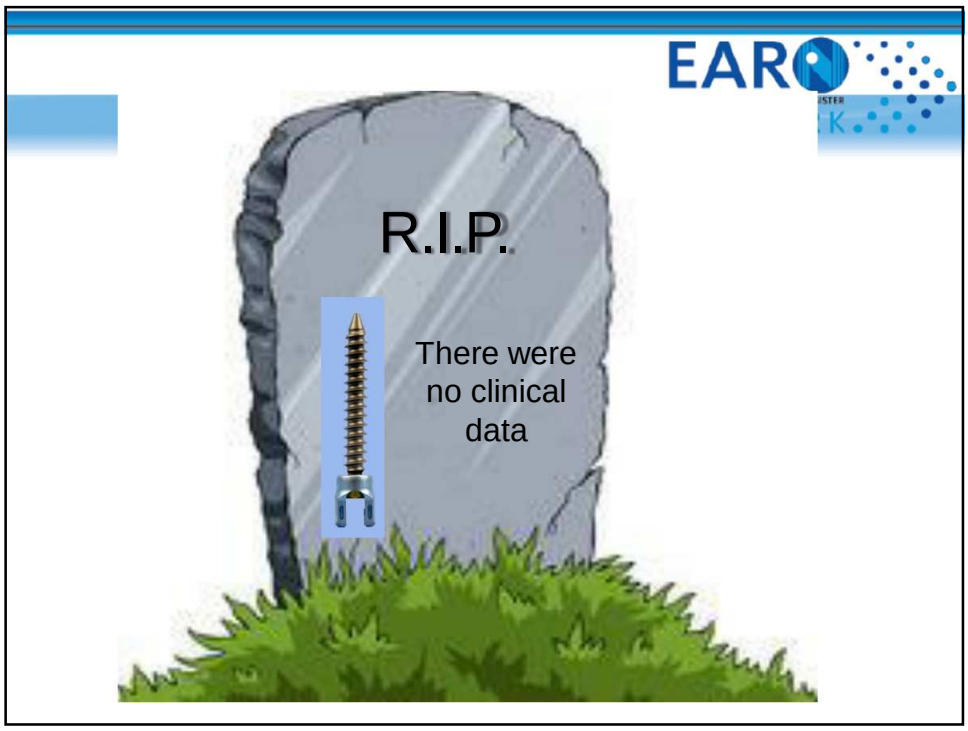
Publications


EARO
R.I.P.
There were no clinical data

March 2014 Requirements in the EU

Register - AHRQ Definition

EAR EUROPEAN ARTHROPLASTY REGISTER NETWORK

"an **organized system** that uses **observational study methods** to collect **uniform data** (clinical or other) to evaluate specified **outcomes** for a **population** defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy **purpose(s)**"

ENT
es iNiTiative

IMDRF International Medical Device Regulators Forum

PROPOSED DOCUMENT

International Medical Device Regulators Forum

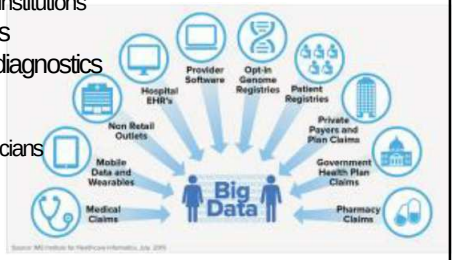
Title: Clinical evaluation

Authoring Group: Medical Device Clinical Evaluation Working Group

Date: 5 April 2019

Registries

- **In fact any data collection without defined termination**
- Examples:
  - Quality/Patient Registries (well known in arthroplasty, cardiology, others in development)
    - National
    - Regional
    - Local, institutional (hospital routine documentation)
    - By Manufacturers
  - Reimbursement and discharge data
    - „Sick funds“
    - Internal quality monitoring at public health institutions
  - Data generated by active medical devices
  - Telemedicine related to medical devices/diagnostics
    - In development (apps)
    - Monitoring of pacemakers
    - Monitoing of diagnostic measures by physicians
  - Surveys based on Internet
  - Cohort studies
  - …….



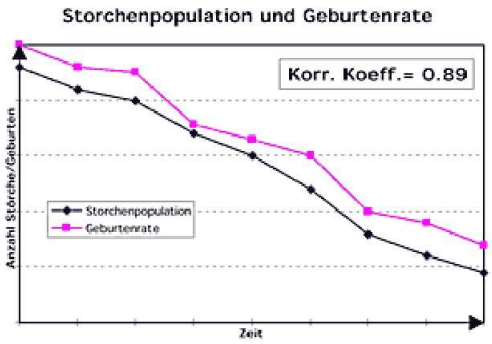
Examples

- Non Active Devices ➔Quality Registries, Customer Feedback like stuctured Surveys,
- Active Medical Devices ➔Data from the devices use/framework (ICU)
- Software ➔generate data by use

- All devices:
  - Discharge records
  - Hospital internal system
  - Payers (Sick Funds, AOK, Medicare)

- **Every Company/Device need it´s own solution**

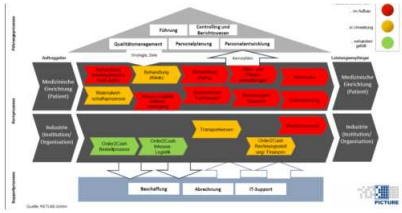
RegistiesStork Population and Birth Rate in Euro



- RWE:
- good tool to detect Correllation

- Causality
  ➔process assessment insufficient
  ➔expert know how in medical field

The Process Perspective



PMS and RM

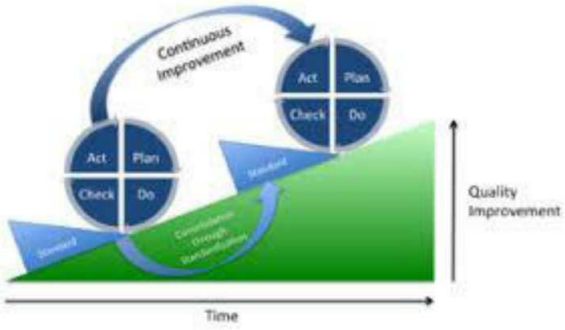
The manufacturers should:

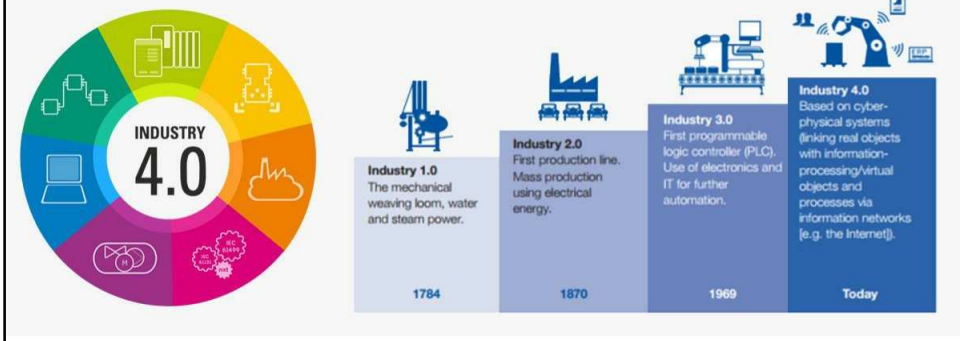
- establish a comprehensive post-market surveillance (PMS) system
- set up under the quality management system
- and based on a PMS plan.

*

PMS and RM

- More and better Clinical Data by PMS required:
- Link with QM-System
- Structured development rather than flash of genius
- Not „only“ device, also training, use of device,….





Clinical Data + Process Perspective

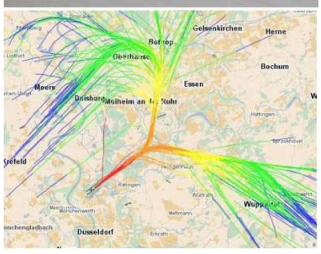
Design | Production | Risk Management | Use of Device | Patients

Health System/Access to Device | ……

Clinical Data provide information on the outcome of the entire treatment chain
➔„final validation“

Processes to Utilize Big Data

- MDR requests implementation of procedures already standard in other industries since > decade



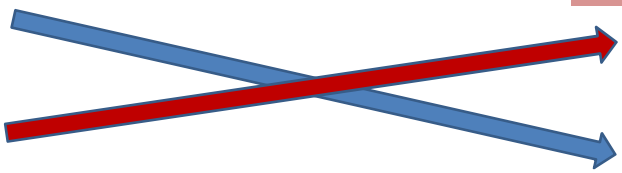
Evaluation of Clinical Data

Confounders

Statistics
(N Patients, Data – Nominal, ordinal. Metric,.)

Methodology
(Selection Bias, Documentation Bias,…)

Treatment Outcome
(Users, Patients, Implantation,…)



RCT

Pharma

Internal Validity

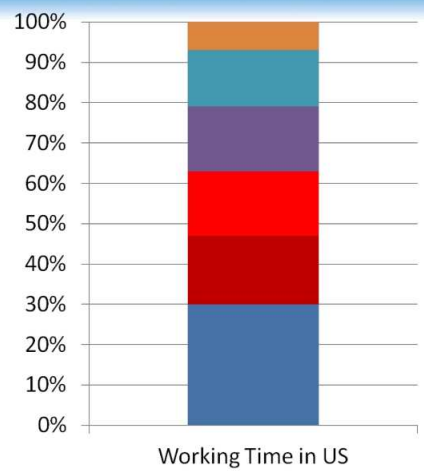
Metaanalyses

Follow Up Studies

Registries

Med. Dev.

External Validity



Management

Input of Experience

Communication

Data Evaluation

Data Entry

Manual Work / Machines

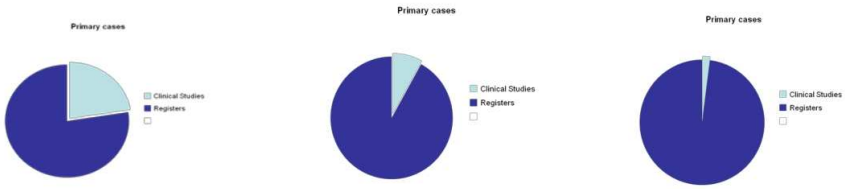
Clinical Data to be considered in the future

Proportion of Activities in at working time (average),

Source: McKinsey, Spiegel

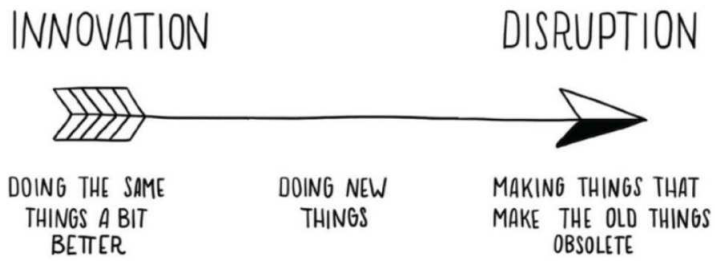
Proportion of new data

Total Knee Arthroplasty, high quality outcome registries only



2010 2015 2025

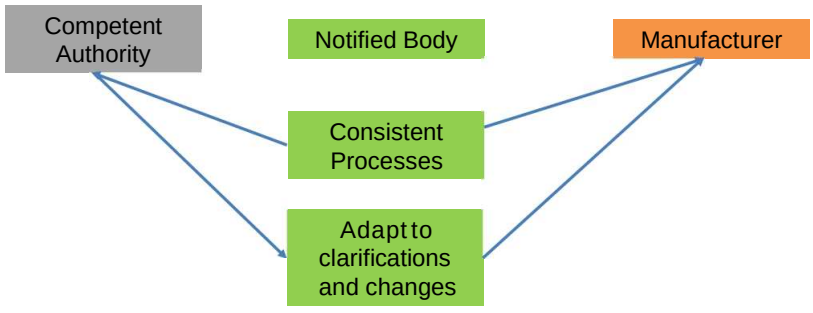
Innovations vs Disruption??



- New datasets
- New funding lines for manufacturers + data suppliers.
- Internal processing and to meet requirements

Interaction

- NB has to be involved in any dervice with relevant potential risks.



Implementation at NB´s

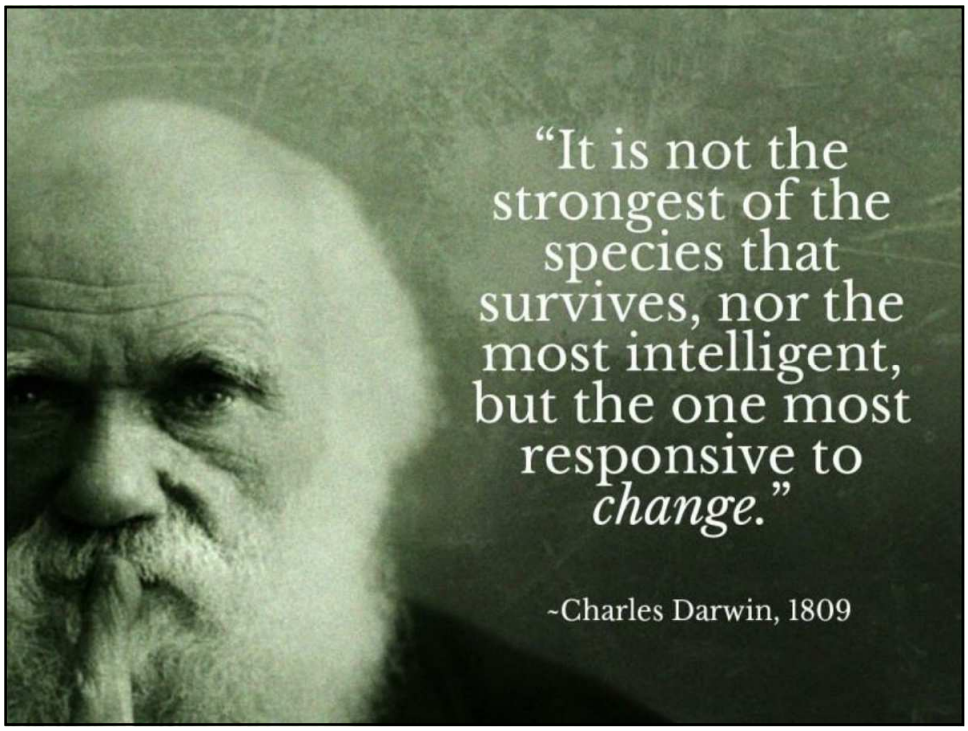
- Concept to realize new requirements
- Strucure inside the NB´s
  - Cooperation with Audits, certification body etc.
  - Decision making
  - Adaption to monitor implementation of Industry 4.0
- NB´s are dependent on agreement with Competent Authorities

Which Registries for Which Clinical Question

- Clinical Data have to be provided, Registry data are one option to do that
- Registry data = less expensive, if data are available
  Data collection = most expensive part of an investigation
- Are adequate routine data available?
- Entire spectrum of big data is available.

Collaboration with HTA

- Procedures in data evaluation are different between RCT´s and Big Data Analyses.
- Registry data can contribute to HTA evaluations.
- Aims for regulatory processes are different from HTA
  - NB´s: Safety and Performance exclusively
  - HTA: wider scope, after CE-approval
- Basic procedures for objective evaluation of Big Data for Medical Devices have to be developed.
- HTA can contribute with highly valuable know how



MEDICAL VALUE
BY **MEDICAL VALLEY**

MEDICAL VALLEY
Europäische Metropolregion Nürnberg

Global Cardiac Implant Registries: A Critical Analysis

EUnetHTA Task Force on HTA and Medical Devices
2nd Workshop, Vienna, May 28th, 2019

Prof. Dr. Peter Kolominsky-Rabas, MD, MBA
Professor of Health Technology Assessment
Interdisciplinary Center for Health Technology Assessment (HTA) and Public Health
Friedrich-Alexander-University Erlangen-Nürnberg
National Cluster of Excellence ‚Medical Technologies - Medical Valley EMN'

National Cluster of Excellence for Medical Technologies

SPONSORED BY THE
Federal Ministry of Education and Research

- public-private partnership (universities, manufacturers, research institutes)
- funded by the German Ministry of Research (BMBF)

Agenda

- Cardiac implants as high-risk medical devices
- Methods
- Results
- Political Framework

Einer geht noch: Der FC Bayern in der Krise › Sport

Süddeutsche Zeitung

NEUESTE NACHRICHTEN AUS POLITIK, KULTUR, WIRTSCHAFT UND SPORT

WWW.SÜDDEUTSCHE.DE | HF3 | MÜNCHEN, MONTAG, 26. NOVEMBER 2018 | 74. JAHRGANG / 48. WOCHE / NR. 273 / 3,30 EURO

Das Streiflicht

VON CHRISTINA BERNDT, KATRIN LANGHANS UND FREDERIK OBERMAIER

Implant Files

Risiko Implantat

Herzschrittmacher, Knieprothesen oder Brustimplantate sollen eigentlich das Leben verbessern. Doch immer mehr Menschen leiden unter gefährlichen Produkten. Sie sind Opfer eines Milliardengeschäfts

Süddeutsche Zeitung Nr. 273, Dienstag, 27. November 2018 HF2

IMPLANT FILES

DAS GEFÄHRLICHE GESCHÄFT MIT DER GESUNDHEIT

Totalausfall

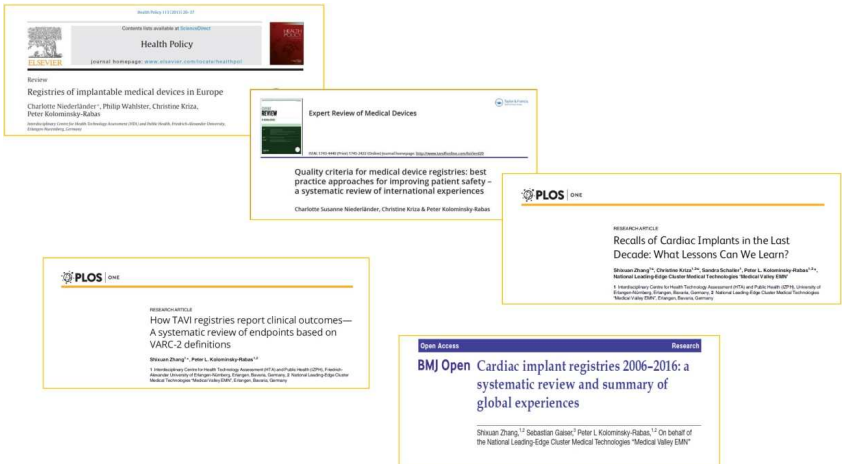
Eine Wirbelsäulenprothese versagt im Test mit Affen. Sie versagt auch im Test mit Menschen. Und trotzdem bringt der Hersteller sie auf den Markt – wo sie wieder versagt. Über einen Medizinskandal, der viele Menschen ihre Gesundheit gekostet hat

VON MAXIMILIAN FERSTL, KATRIN LANGHANS, FRANZISKA VON MALSEN UND FREDERIK OBERMAIER
FOTO: STEFANIE PREUIN

Thomas Weske hätte – nach allem, was man heute weiß – seine Wirbelsäulenprothese nie eingesetzt werden dürfen.

Methods

2013-2018 five Systematic Reviews
Special focus on Cardicac Implant Registries



Global Recalls of Cardiac Implants 2004-2014

Table 1. Number of cardiac implants and total recall reports.

Regulatory Authorities	Total cardiac implant recalls	Total recall report	Time period availability
U.S. Food and Drug Administration (FDA)	12	335	2004–2014
Canada. Health Canada (HC-SC)	10	2486	2005–2014
Australia. Therapeutic Goods Administration (TGA)	12	1050	2012–2014
New Zealand. Medicines and Medical Devices Safety Authority (Medsafe)	3	723	2012–2014
UK. Medicines and Healthcare Products Regulatory Agency (MHRA)	24	554	2004–2014
Ireland. Health Products Regulatory Authority (HPRA)	3	149	2004–2014
Switzerland. Swiss Agency for Therapeutic Products (Swissmedic)	67	3697	2005–2014
Germany. Federal Institute for Drugs AND Medical Devices (BfArM)	96	6632	2005–2014
PR China. China Food and Drug Administration (CFDA)	6	195	2010–2014
China Hong Kong Health Department	29	788	2005–2014
Saudi Arabia. Saudi Food and Drug Authority (SFDA)	38	5103	2011–2014

Table 1 indicates the number of recall reports in eleven regulatory authorities within the fixed time period, including total numbers of recall reports and total numbers of cardiac implants recall reports. This table aims to give readers an overall impression the medical device recalls situation.

doi:10.1371/journal.pone.0125987.t001

in total 300 cardiac implant recalls

Zhang et al. Recalls of Cardiac Implants in the Last Decade: What Lessons Can We Learn? PLOS ONE (2016)

Recall Reasons of Cardiac Implants

Table 2. Ratio of recall reasons among cardiac implant medical devices.

Categorizes	Sub-categorizes	ICD	CRT	Pacemaker	Stent	Leads	Implantable artificial organs	Total Number
Battery	Capacitor	10	6					16
	Voltage	2						2
	Connection	2	1				1	4
	Battery defect	3						3
	Reporting			2				2
	Premature battery depletion	4	2	1				7
Software	Performance inconsistency problem	5	1	1				7
	Inappropriately set	2	1	1				4
	Lead to battery defect	2		2				4
	Influence by environment			1				1
Output data	Incorrect express	1		1				2
	No output			1				1
	No or incorrect feedback						2	2
Therapy delivery	Background influence	1						1
	Pacing inhibition	4	1					5
	Inappropriate therapy	2		2				4
	Equipment malfunction	3	1		1			5
	Fractured				6	1		7
	Failed or partial deployment				6			6
	Leak			1				1
	Inadequate size				2		1	3
Connection	Weakened bond	1					1	2
	Partially or fully separated						1	1
	Separation of wires			2		2		4
	Bend relief						1	1
	Lead insulation abrasion					5		5
	Materials detached from guide wires					2		2
	Total Number	42	13	15	15	10	8	103

33.0% related to problems with the device battery

32.0% related to problems In therapy delivery

Zhang et al. Recalls of Cardiac Implants in the Last Decade: What Lessons Can We Learn? PLOS ONE (2016)

Cardiac Implant Registries – Objective

Systematic Search 2006-2016

Aim of study	global structure and key elements of cardiac implant registries (CIR)
Timeframe	past decade (2006–2016)
Evidence	Support German legislation Implantateregister-Errichtungsgesetz

Cardiac Implant Registries – Objective

Systematic Search 2006-2016

- Participant criteria
- Research type
- Clinical endpoints
- Follow-up

- Data collection
- Data entry
- Data validation
- Public Access & Transparency

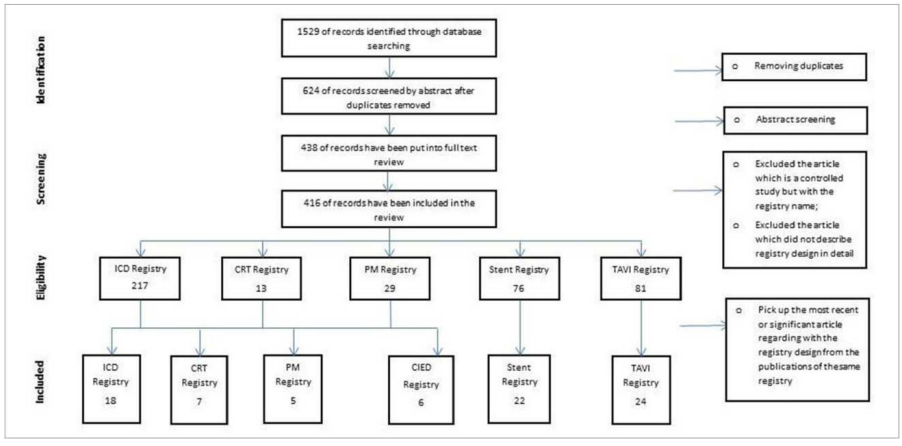
- Ethics
- Funding

Different Types of Cardiac implants

- Battery-based implants
  - Cardiovasc. implantable electronic device (CIED)
  - implantable cardioverter defibrillator (ICD)
  - cardiac resynchronisation therapy (CRT)
  - pacemaker
- Non-battery based implants
  - coronary stents
  - transcatheter aortic heart valve implantation (TAVI)

Cardiac Implant Registries – Methods

Systematic Search 2006-2016



in total 82 cardiac implant registries included in review

Cardiac Implant Registries – Distribution

Systematic Search 2006-2016

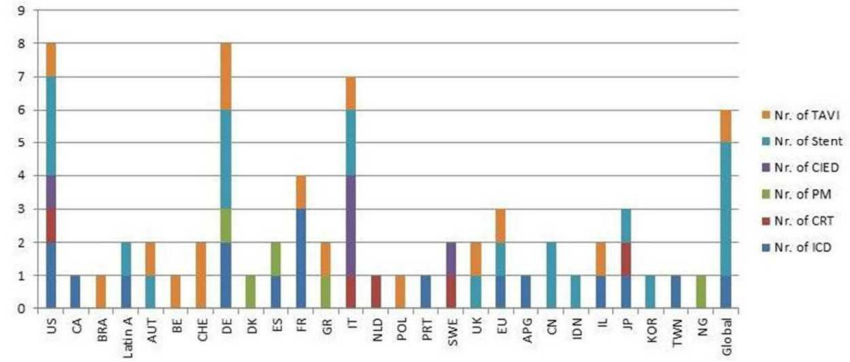


Figure 2 Location of identified cardiac implant registries. CRT, cardiac resynchronisation therapy; CIED, cardiovascular implantable electronic device; ICD, implantable cardioverter defibrillator; PM, pacemaker; TAVI, transcatheter aortic heart valve implantation.

Zhang et al. Cardiac Implant Registries 2006-2016. BMJ Open (2018)

Clinical Endpoints used in CIR

TAVI Registries (n = 24)

- 2011 and 2013 — Valve Academic Research Consortium (VARC) published international standardized definitions on reporting endpoints in TAVI studies
- Key reporting element — 30-day cardiovascular mortality; 1-year mortality

Clinical Endpoints used in TAVI Registries

Study	All-cause mortality (30 days)	Cardiovascular mortality (30 days)	Mortality (1 year)
Balloon-expandable Sapien Prosthesis Registry			
The iTER Registry	137 (7.2)	-	286 (15.0)
The PARTNER II SAPIEN 3 Registry			
- HR/inoperable	13 (2.2)	8 (1.4)	-
- IR	12 (1.1)	10 (0.9)	-
A Spanish single center TAVI Registry	(12.7)	(6.35)	(25.4)
The Swiss TAVI Registry			
-Sapien 3	5 (3.3)	4 (2.6)	-
-Sapien XT	20 (4.5)	19 (4.3)	-
Rouen TAVI Registry	11 (4.7)	-	(23.2)
The SOURCE ANZ Registry	10 (7.8)	-	23 (17.8)
Self-expandable CoreValve Prosthesis Registry			
The Italian CoreValve Registry	80 (6.1)	62 (4.7)	-
Mixed Registry			
WIN-TAVI Real-World Registry	40 (3.4)	38 (3.3)	-
The Pooled-Rotterdam-Milano-Toulouse Registry	10 (6.0)	8 (4.8)	-
The Asian TAVR Registry	21 (2.5)	14 (1.7)	81 (10.8)
Inohara et al. 2016			
The Japan OCEAN TAVI Registry	0 (0)	0 (0)	-
Nassy database	1 (0.6)	1 (0.6)	-
TAVI-Karlsruhe Registry			
-TA	(6.1)	(4.1)	-
-TF	(6.5)	(5.1)	-
The Brazilian Registry	(9.1)	(7.9)	(21.5)
PRAGMATIC Multicenter Study	63 (5.9)	56 (5.3)	187 (18.5)
Multicenter registry from America and Europe	65 (5.7)	-	-
The Royal Prince Alfred Hospital TAVI Program	3 (3.0)	2 (2.0)	7 (7.0)
The University Hospital Zurich TAVI Registry	32 (9.1)	31 (8.7)	(21.0)
Other TAVI System			
Nordic Lotus-TAVR registry	3 (1.9)	-	-
DISCOVER Study	1 (1.0)	1 (1.0)	10 (10.0)

Zhang et al. How TAVI-Registries report Clinical Outcomes PLOS ONE (2017)

1-year mortality

Reported only by

55% of registries

Public Accessibility and Transparency

- 7% (n = 6!) can be accessed via a web page, along with an annual report
- 93% neither have a web-site available to the public nor an annual report
- Identification via research publications only

  often not accessible to patients and public
- Any or very limited informationon methods/ registry design

Summary

■ Intransparent to researchers	Limited informationon registry methods i. e. inclu./exclu, criteria, data collection
■ Intransparent to payers	Insufficient reporting of clinical endpoints i. e. long-term outcomes
■ Intransparent to patients	Limited access to data for patients and public

Current situation

■ European Commission
Medical Device Directive – May 2017

Article 108

Device registers and databanks

The Commission and the Member States shall take all appropriate measures to encourage the establishment of registers and databanks for specific types of devices setting common principles to collect comparable information. Such registers and databanks shall contribute to the independent evaluation of the long-term safety and performance of devices, or the traceability of implantable devices, or all of such characteristics.

Current situation

- European Commission
  FunctionalSpecifications – April 2019

EUROPEAN COMMISSION
Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs
Consumer, Environmental and Health Technologies
Health Technology and Cosmetics

Contact: GROW-EUDAMED-ADMINISTRATOR@ec.europa.eu

mailto:GROW-EUDAMED-ADMINISTRATOR@ec.europa.eu

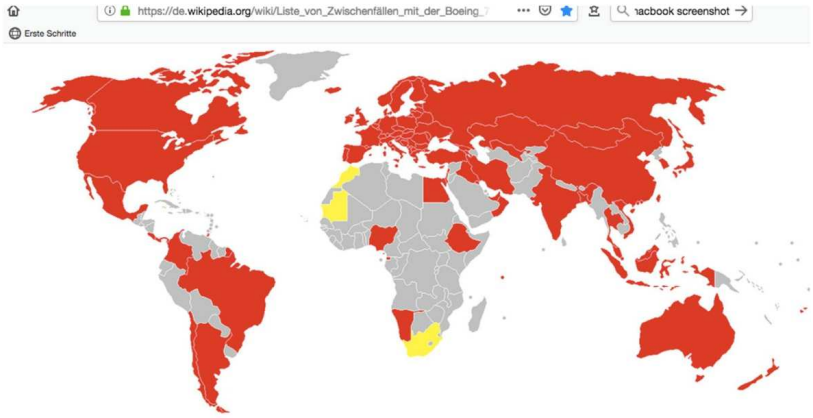
28/02/2019

Draft Functional specifications for the
European Database on Medical Devices (Eudamed) -
First release (High(1)) to be audited

First draft consolidated version of functional specifications for Eudamed (version 4.1)

European Commission, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË - Tel. +32 22991111

Ethiopian Air Crash | Why are Boeing 737 max crashin...



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Home » ASN Aviation Safety Database » Type Index

Accident list: Boeing 737

Last updated: 26 May 2019

213 occurrences in the ASN safety database, showing occurrence 201 - 213

1 2 3

date	type	registration	operator	fat.	location	pic	cat
13-SEP-2016	Boeing 737-347 (SF)	PK-YSY	Trigana Air Service	0	Wamena Airpo...		A1
28-MAR-2017	Boeing 737-3M8	OB-2036-P	Peruvian Airlines	0	Jauja-Franci...		A1
31-MAY-2017	Boeing 737-33A	PK-CJC	Sriwijaya Air	0	Manokwari-Re...		A1
18-JUL-2017	Boeing 737-301 (SF)	PK-YGG	Tri-MG Airlines	0	Wamena Airpo...		A1
13-JAN-2018	Boeing 737-82R (WL)	TC-CPF	Pegasus Airlines	0	Trabzon Airp...		A1
17-APR-2018	Boeing 737-7H4 (WL)	N772SW	Southwest Airlines	1	near Philadelphia...		A1
18-MAY-2018	Boeing 737-201	XA-UHZ	Cubana, Isf Global Air	112	near Havana-José ...		A1
16-AUG-2018	Boeing 737-85C (WL)	B-5498	Xiamen Airlines	0	Manila-Ninoy...		A1
01-SEP-2018	Boeing 737-8AS (WL)	VQ-BJI	UTAir	0	Adler/Sochi ...		A1
28-SEP-2018	Boeing 737-8BK (WL)	P2-PXE	Air Niugini	1	Chuuk/Weno I....		A1
29-OCT-2018	Boeing 737 MAX 8	PK-LQP	Lion Air	189	near Tanjung Bungin		A1
10-MAR-2019	Boeing 737 MAX 8	ET-AVJ	Ethiopian Airlines	157	near Addis Ababa-...		A1
03-MAY-2019	Boeing 737-81Q (WL)	N732MA	Miami Air International	0	Jacksonville...		A1

1 2 3

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Home » ASN Aviation Safety Database » Type Index

Accident list: Boeing 737

213 occurrences in the ASN safety database, showing occurrence 1 - 100

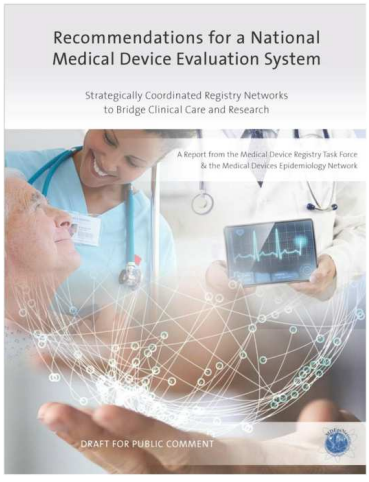
1 | 2 | 3

date	type	registration	operator	fat.	location	pic	cat
19-JUL-1970	Boeing 737-222	N9005U	United Airlines	0	Philadelphia,...		A1
08-DEC-1972	Boeing 737-222	N9031U	United Airlines	43+ 2	near Chicago-Midw...		A1
31-MAY-1973	Boeing 737-2A8	VT-EAM	Indian Airlines	48	near Delhi-Indira...		A1
31-MAR-1975	Boeing 737-247	N452TW	Western Air Lines	0	Casper Airpo...		A1
04-DEC-1977	Boeing 737-2H6	9M-MBD	MAS	100	near Tanjong Kupang		H1
11-FEB-1978	Boeing 737-275	C-FPWC	Pacific Western	42	Cranbrook Ai...		A1
02-APR-1978	Boeing 737-2A1	PP-SNX	VASP	0	São Paulo-Co...		A1
04-APR-1978	Boeing 737-229C	OO-SDH	Sabena	0	Charleroi-Ge...		A1
17-DEC-1978	Boeing 737-2A8	VT-EAL	Indian Airlines	1+ 3	Hyderabad-Be...		A1
26-APR-1979	Boeing 737-2A8	VT-ECR	Indian Airlines	0	Madras Airpo...		C1
04-NOV-1980	Boeing 737-2M2C	D2-TAA	TAAG	0	Benguela Air...		A1
17-FEB-1981	Boeing 737-2Y3	N468AC	Air California	0	Santa Ana-Ja...		A1
22-AUG-1981	Boeing 737-222	B-2603	FEAT	110	near Miao-Li		A1
13-JAN-1982	Boeing 737-222	N62AF	Air Florida	74+ 4	near Washington-N...		A1
25-MAY-1982	Boeing 737-2A1	PP-SNY	VASP	2	Brasilia Int....		A1
26-AUG-1982	Boeing 737-2Q3	JA8444	Southwest Air Lines	0	Ishigaki Air...		A1
22-FEB-1983	Boeing 737-2A1C	PP-SNC	VASP	2	Manaus-Eduar...		A1
27-MAR-1983	Boeing 737-2B1	C9-BAB	LAM	0	near Quelimane Ai...		A1
11-JUL-1983	Boeing 737-2V2	HC-BIG	TAME Ecuador	119	near Cuenca		A1
23-SEP-1983	Boeing 737-2P5	A4O-BK	Gulf Air	112	Mina Jebel Ali		C1
08-NOV-1983	Boeing 737-2M2	D2-TBN	TAAG	130	near Lubango Airp....		C1

MEDICAL VALLEY EMN

Long- term follow-up in postmarket surveillance

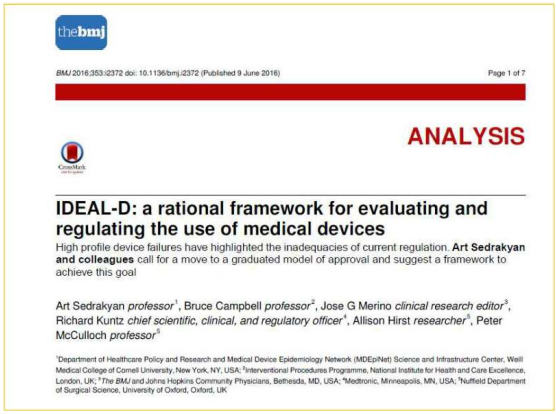
- US
- 2015
- The Medical Device Epidemiology Network issued
  'Recommendations for a National Medical Device Evaluation System'



MEDICAL VALLEY EMN

Decision-Makers:
Long- term surveillance is feasible

Sedrakyan et al. BMJ 2016



thebmj

BMJ 2016;353:i2372 doi: 10.1136/bmj.i2372 (Published 9 June 2016)

ANALYSIS

IDEAL-D: a rational framework for evaluating and regulating the use of medical devices

High profile device failures have highlighted the inadequacies of current regulation. **Art Sedrakyan and colleagues** call for a move to a graduated model of approval and suggest a framework to achieve this goal

Art Sedrakyan *professor*[1], Bruce Campbell *professor*[2], Jose G Merino *clinical research editor*[3], Richard Kuntz *chief scientific, clinical, and regulatory officer*[4], Allison Hirst *researcher*[3], Peter McCulloch *professor*[5]

[1]Department of Healthcare Policy and Research and Medical Device Epidemiology Network (MDEpiNet) Science and Infrastructure Center, Weill Medical College of Cornell University, New York, NY, USA; [2]Interventional Procedures Programme, National Institute for Health and Care Excellence, London, UK; [3]*The BMJ* and Johns Hopkins Community Physicians, Bethesda, MD, USA; [4]Medtronic, Minneapolis, MN, USA; [5]Nuffield Department of Surgical Science, University of Oxford, Oxford, UK

Industry:
Increase transparency, foster credibility

Schweigsamer Riese

Der US-Konzern Medtronic ist der weltgrößte Hersteller von Medizinprodukten – aber kaum jemand kennt ihn. Über die dunkle Seite eines Global Players, dessen Erfindungen Leben retten können. Oder zerstören

VON CHRISTINA BERNDT, KATRIN LANGHANS UND FREDERIK OBERMAIER; FOTOS: STEFANIE PREUIN

Beim Kontrollturm flogen die Ärzte zu tuscheln

Conclusion

■ Continuous evaluation	prospective registries from beginning of clinical use
■ „Breakdown statistics“	Regular reporting of malfunction on a monthly basis
■ Long-term data	long-term clinical outcomes detection of late side effects

Thank You for Your time!

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peter.kolominsky-rabas@fau.de

EUnetHTA Task Force on HTA and Medical Devices

MEDDEV 2.7/1 Rev. 4, SSCP and other Guidelines

Tom Melvin

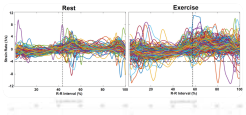
28 May 2019

Vienna

Agenda

- Introduction
- EUDR Implementation
- Implementation at the Clinical WG

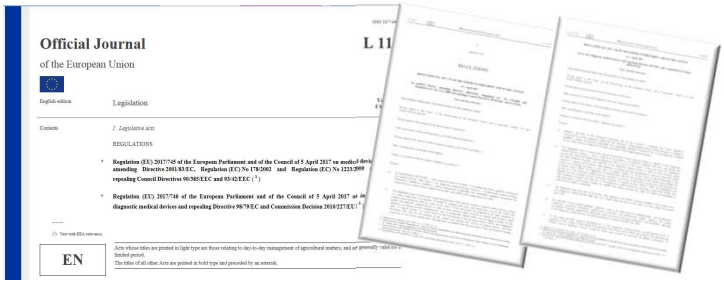
Introduction



Devices are different to Medicinal Products

- Approximately 20,000 MP
- Approximately 500,000 Medical Device products
- Develop by iteration
- Scientific Developments

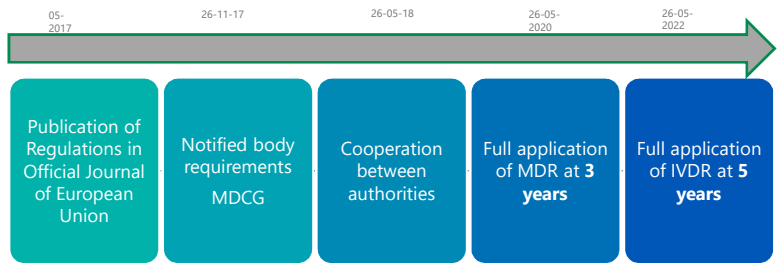
Regulation (EU) 2017/745 & 2017/746



Key elements of MDR changes

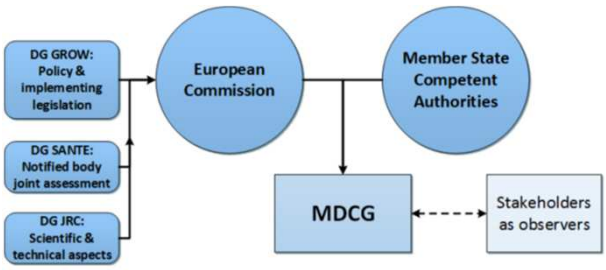
- Better performing **notified bodies** - enhanced requirements for notified bodies and their oversight by authorities
- Enhanced **market surveillance** – defined requirements, improved systems and obligations for manufacturers and for authorities
- Clearer **criteria for high risk devices** – clinical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

Transition period

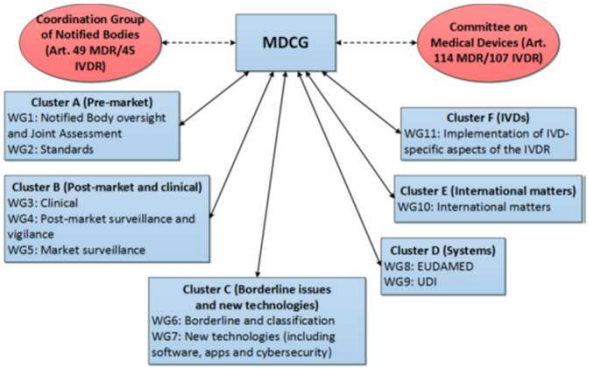


Implementation EUDR

European Co-ordination



MDCG Working Groups



CAMD Implementation Roadmap

1. Clinical Evaluation & Clinical Investigation (MD); Performance Evaluation & Performance Studies (IVD)

	Activity	Recommended responsible parties/owners	Priority level
1.1	**Clinical evaluation work package** • Guidance on equivalence, well established technologies, clinical evidence • Gap analysis of MEDDEV 2.7/1 • Contribution to relevant Implementing Acts (IA) • Work on interface between various documents/reports e.g. CER, SSCP, PSUR. • Contribution to guidance on performance evaluation and clinical evidence for IVDs	• CIE WG • IVD WG	High
1.2	**Template document development (see also 4.4)** • Summary of Safety and Clinical Performance (SSCP) [MD] • Summary of Safety and Performance [IVD] • Clinical Evaluation Assessment Report (MD) • Performance evaluation plan and performance evaluation report (IVD) • Clinical Investigation application form (MD) • CI Assessment Report (MD) • Performance study Application Form (IVD) • Performance Study Report (IVD) • SAE/device deficiency reports and timelines (MD and IVD) • PMCF plan and PMCF report (MD) • PMPF plan and PMPF report (IVD)	• CIE WG • IVD WG • NBOG • EUDAMED WG	Medium – High

COM 'Rolling Plan' for EUDR Implementation

MDR / IVDR - IMPLEMENTATION ROLLING PLAN

This Rolling Plan contains the list of identified essential implementing acts, actions and guidance to be put in place by the Commission and/or the MDCG during the transitional period together with relevant information on expected timelines and state-of-play. The information is organised into two main sections (implementing acts; other actions/initiatives). The document will be subject to quarterly review in order to provide the authorities and stakeholders with the most updated information. This document shall be read in conjunction with the "MDR/IVDR roadmap", produced by the Competent Authorities for Medical Devices project (CAMD) in cooperation with the Commission (and available at https://www.camd-europe.eu/regulatory/medical-devices-regulation-vitro-diagnostics-regulation-mdr-ivdr-roadmap), which contains a much more comprehensive overview of all the initiatives (including guidance) expected to be undertaken during the transitional period by the Commission and the National Competent Authorities

Latest update: April 2019

No.	Subject	Legal basis	Description	Expected timelines (expected date of final adoption/date of accomplishment)	State-of-play/Next step
			IMPLEMENTING REGULATIONS/ACTS		
1	Notified bodies scope of designation	Article 42(13) MDR Article 38(13) IVDR	Implementing Act Definition of the list of codes and corresponding types of devices for the purpose of specifying the scope of the designation of notified bodies. This action is an essential pre-condition for the launch of the designation procedure for Notified Bodies	26 November 2017 (Legal deadline)	Adopted and published on 24 November 2017 COMPLETED
2	Reprocessing of single-use medical devices	Article 17(5) MDR	Implementing Act Common specifications laying down requirements related to reprocessing of single-use devices concerning: — risk management, including the analysis of the construction and material, related properties of the device (reverse engineering) and procedures to detect changes in the design of the original device as well as of its planned application after reprocessing, — the validation of procedures for the entire process, including cleaning steps, — the product release and performance testing, — the quality management system, — the reporting of incidents involving devices that have been reprocessed, and — the traceability of reprocessed devices.	November 2019 It shall be noted that, in the event that those CS are not adopted by 26 May 2020, reprocessing shall be performed in accordance with any relevant harmonised standards and national provisions	Formal public consultation (Q2 2019)

Guidance to Follow

- Implementing Acts
- Harmonised standard (eg. ISO standard)
- MEDDEV / MDCG Guidance
- Common specifications

Clinical requirements – Snapshot

- Common specifications & Scrutiny
- Equivalence
- Justify level evidence
- Consideration of alternatives
- Summary of Safety and Clinical Performance
- Implantable and Class III CI requirements

Other important changes

- Registry data
- Device traceability with UDI / Implant cards
- Summary clinical information in an SSCP
- Central publicly accessible database (Eudamed)

Implementation at Clinical WG

CIE Working Group: MDR Implementation Work Packages

1. Clinical Evaluation
2. SSCP
3. Template & Eudamed
4. CIE / IVD Taskforce

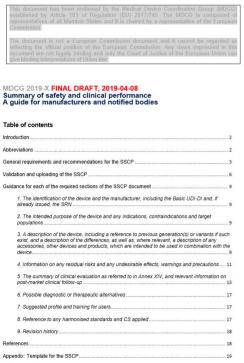
Work Package 1: Clinical

- Draft guidance on equivalence and 'sufficient clinical data'
- Focus on new aspects from MDR and differences between MEDDEV and MDR
- At NCA draft stage. Will be shared with stakeholders as next step

Work Package 2: SSCP

- SE, DK lead WP2
- Guidance and template endorsed at Clinical WG in April
- 7 versions, extensive consultation
- To be presented at MDCG 24 June 2019

SSCP: Guidance + Template



No 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 the preliminary views of the MDCG and do not bind the European Commission and any binding interpretation of Union law.

MDCG 2019-X **FINAL DRAFT, 2019-04-08**

Summary of safety and clinical performance
A guide for manufacturers and notified bodies

Table of contents

Appendix: Template for the SSCP
Texts in *italic* in the template are general information texts proposed to be included in the SSCP document.

Note that there shall always be SSCP information dedicated to users/healthcare professionals for all implantable devices and for all class III devices, other than custom-made or investigational devices. When relevant, a second part dedicated to patients/lay persons should be added. See further recommendations on relevant SSCP information for patients in this guide.

Summary of safety and clinical performance

This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The SSCP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

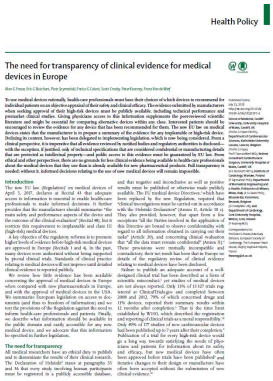
If the SSCP includes a part intended for patients, the following can be added:
Following this information there is a summary intended for patients.

1. Device identification and general information
   1.1. Device trade name(s)
   1.2. Manufacturer, name and address
   1.3. Manufacturer single registration number (SRN)
   1.4. Basic UDI-DI
   1.5. Medical device nomenclature description / text
   1.6. Class of device
   1.7. Year when the first certificate (CE) was issued covering the device
   1.8. Authorised representative if applicable; name and the SRN
   1.9. NB's name (the NB that will validate the SSCP) and the NB's single identification number
2. Intended use of the device
   2.1. Intended purpose
   2.2. Indication(s) and target population(s)
   2.3. Contraindications and/or limitations

Work Package 3: EUDAMED, templates, Co-ordinated CI Assessment

- Eudamed functional specifications
- Templates, including CI application / assessment, CEAR, SAE
- Facilitate exchange of experience on co-ordinated CI assessments
- Initial work on transparency to facilitate Eudamed clinical portal development

Fraser et al, Lancet July 2018



Health Policy

The need for transparency of clinical evidence for medical devices in Europe

Transparency

- Eudamed + public access
- UDI device traceability
- Implant cards
- SSCP
- Clinical investigation report and summary

Work Package 4: IVD-CIE Co-operation

Guidance on performance evaluation

Sharing of guidance and experience

Joint Action on Market Surveillance

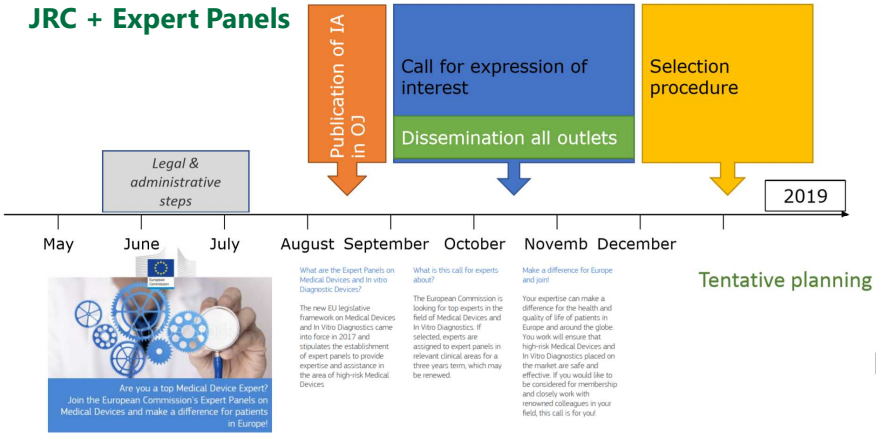
Member state communication

Market surveillance co-operation

Clinical resources

Common specification prioritisation

JRC + Expert Panels



I	Orthopaedics, traumatology, rehabilitation, rheumatology	1	Joint replacements (hip, knee, shoulder)
		2	Spinal devices
		3	Non-articulating devices, rehabilitation
II	Circulatory system	4	Prosthetic heart valves and devices for heart valve repair
		5	Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses
		6	Active implantable cardiac devices and electrophysiological devices
		7	Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices)
		8	Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts (and left ventricular assist devices)
III	Neurology	9	Central and peripheral nervous system devices
		10	Implants for hearing and vision (sensory recovery)
		11	Neurosurgical devices
IV	*Respiratory, Anaesthesiology, Intensive Care*	12	Respiratory and anaesthetic devices
V	*Endocrinology and Diabetes*	13	Endocrinology and diabetes (e.g. insulin delivery systems and closed-loop systems, continuous glucose monitoring) implantable systems
VI	*General and Plastic Surgery, Dentistry*	14	Surgical implants and general surgery
		15	Plastic surgery and wound care
		16	Maxillofacial surgery
		17	Dentistry (Devices for dentistry (oral surgery, implantology, dental materials incl.))
VII	*Obstetrics & Gynaecology including Reproductive Medicine*	18	Devices for obstetrics and gynaecology
VIII	*Gastroenterology & Hepatology. Nephrology & Urology*	19	Devices for gastroenterology and hepatology
		20	Devices for nephrology and urology
IX	*Ophthalmology*	21	Devices for ophthalmology
X	In-vitro diagnostic medical devices (IVD)	22	IVD devices

Thank you

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innovationoffice@hpra.ie

Wrap up by Claudia Wild:

There is a difference between clinical benefit and added benefit. More communication is needed to clarify. 1st DG (GROW) has indicated of being occupied with the regulation, therefore we need to increase our visibility even more. 2nd DG (SANTE) has indicated a production of 5 assessments per year in the sustainable network (2022+). We are better, and we can do more, HTA is here to stay. We are committed to a sustainable health system; we only want products that have a proved effect for patients.