3rd Workshop of the EUnetHTA Task Force on HTA and Medical Devices

November 4th, 2020 online meeting

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

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

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EUnetHTA Task Force (TF) members:

Lead of TF:

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

Members of TF (inputs):

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
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13. Hannah Brühl (G-BA) – G
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17. Dimitra Lingri (EOPPY) – GR
18. Iñaki Gutierrez-Ibarluzea (Osteba) – ES
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21. Patricia Harrington (HIQA) – IE
22. Mirella Marlow (NICE) – UK
23. Patrice Chalon (KCE) – BE
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 3rd workshop of the EUnetHTA Task Force on HTA and Medical Devices. The initiative to organize this workshop (and 2 earlier ones in 2018 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 are synergies between the regulators and Health Technology Assessment.

The aims of the 3rd 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 the regulation for the European HTA collaboration as basis to explore synergies between regulation and HTA.
2. to provide a platform for a dialogue on topics about specific technologies that are relevant to MDR and HTA, with the focus on the evaluation of software that is classified as high risk device and to explore the added value and appropriate ways of a dialogue on these issues for all parties.

Session 1 “Update: Status Quo of the Implementation of MDR/IVDR and of European HTA” 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 and its progress in legislation. Presentations are given by EC-representatives of DG Sante´ responsible for the two regulations, a national representative and co-chair of the CIE/ Clinical Investigation and Evaluation working group and a representative of Notified Bodies, director of Team-NB.

Session 2 “Appropriate Evidence for Regulation and HTA for Software Classified as High Risk Medical Devices” is intended to inform about the guidance from regulators, guidance and experiences from HTA bodies on the evaluation of software (e. g. decision support systems for diagnosis, prognosis, monitoring, treatment) falling under the class of high risk medical devices. Presentations are given by a representative of MDCG/ Medical Device Coordination Group, Chair of MDCG Working Group New Technologies, by a representative of a Notified Body, the Global Director Functional Safety, Software and Digitization/ TÜV SÜDs, by a representative of a national HTA-agency, the Associate Director - Medical Technologies Evaluation Programme and Interventional Procedures Programme/ NICE UK, by a representative of clinicians, Chair of Regulatory Affairs Task Force of the Biomedical Alliance in Europe, by a clinical researcher of the University of Cambridge and by a representative of industry Cardiology GE Healthcare).

Workshop housekeeping rules

- All attendees have been joined to this session in listen-only mode.
  - Please do not try switching your webcam or microphone on. Only presenters are enabled to do so themselves.
- You can use the “view options” setting on your own device to adjust the view of your Zoom window.
- Please submit questions to the panelists via the Q&A feature by sending your question with option “everyone”, so all speakers and attendees can see all questions.
- Questions will be brought to the panelists’ attention by the moderator (Julia) and answered live at the end of each presentation.
- Chat feature is disabled for attendees.

eunethta

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Morning Agenda

9.15-9.30	Registration, Technical issues
9.30-9.45	Welcome and Introduction to Aim of Workshop Claudia Wild, Director of Austrian Institute for Health Technology Assessment
Session 1	***Status Quo of the Implementation of MDR/IVDR and of European HTA. Possible Synergies*** *Presentations*
9.45-10.00	The EU Legal Framework for Medical Devices: Current Status of Implementation of the Two Regulations. Lessons Learned from COVID-19. Anna-Eva Ampelas, DG SANTE
10.00-10.15	EU Cooperation on HTA beyond 2020 - European Commission Proposal to Strengthen EU Cooperation on HTA. Current Status Quo, Possible Collaboration with Regulators. Lessons Learned from COVID-19. Flora Giorgio, DG SANTE
10.15-10.30	Q & A for Both Talks
10.30-10.40	Break
10.40-11.00	Implementation of the MDR by Templates of the CIE Working Group Tom Melvin, Co-chair of the CIE, Health Products Regulatory Agency, Ireland
	Q & A
11.00-11.20	Status quo of Implementation of the MDR/IVDR from the Perspective of Notified Bodies Françoise Schlemmer, Director Team-NB Notified Bodies Association
	Q & A
11.20-12.20	Lunch break

Afternoon Agenda

Session 2 Part 1	***Appropriate Evidence for Regulation and HTA for Software Classified as High Risk Medical Devices.*** *Presentations and Moderated Discussion*
12.20-12.40	Introduction to Classification of Software as (High-risk) Medical Device and on the MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/ Performance Evaluation (IVDR) of Medical Device Software Nada Alkhayat, Chair MDCG Working Group New Technologies
	Q & A
12.40-13.00	Experiences of Notified Bodies with Software Evaluation Under the MDDs and Challenges Under the MDR Abtin Rad, Global Director Functional Safety, Software and Digitization, Responsible for TÜV SÜDs activities around "Artificial intelligence", "Cybersecurity" and "Software" in Medical Devices.
	Q & A
13.00-13.20	The Framework for ehealth and Experiences from HTA Bodies of the Assessment of Software Classified as High Risk Medical Device Joanne Holden, CHTE Associate Director - Medical Technologies Evaluation Programme and Interventional Procedures Programme, National Institute of Health and Care Excellence, UK
	Q & A
13.20-13.40	Break

Afternoon Agenda

Session 2 Part 2	***Appropriate Evidence for Regulation and HTA for Software Classified as High Risk Medical Devices.*** *Presentations and Moderated Discussion*
13.40-14.00	Machine Learning Algorithms in Cardiology, Evaluation Needs and Challenges From the Perspective of the Clinician Alan Fraser, Chair, Regulatory Affairs Task Force of the Biomedical Alliance in Europe
	Q & A
14.00-14.20	Overview on Study Designs for Clinical/Other Studies for the Evaluation of the Artificial Pancreas Roman Hovorka , Prof of Metabolic Technology, University of Cambridge
	Q & A
14.20-14.40	Overview of Developments of Integration of Machine Learning into Diagnostic or Decision-support Software, Challenges for Clinical Evaluation from the Perspective of the Developer/ Manufacturer Eigil Samset, Chief Technology Scientist, Cardiology GE Healthcare
	Q & A
14.40-15.15	Moderated Panel Discussion and Questions from the Audience Chair: Tom Melvin, Moderator: Julia Chamova
15.15-15.30	Wrap up and Outlook to Next Activities Claudia Wild, Austrian Institute for Health Technology Assessment

3rd Workshop of the EUnetHTA Task Force on HTA and Medical devices Nov 4th, 2020

Introdution and Aim of Workshop

Claudia Wild, Director AIHTA, WP4-Co-Lead

2017: Development of Vision Paper Establishment of Task Force

Vision Paper

for coordinated activities
of HTA and Medical Device authorities

Date start: August 2017
living document

EUnetHTA Task Force HTA and MDR:

Claudia Wild (AIHTA) – AT (strategic tasks)
Petra Schnell-Inderst (UMIT) – AT (operational tasks)

KCE – Belgium, IQWiG – Germany, G-BA – Germany, HAS – France, EOPPY – Greece, HIQA – Irland, AGENAS – Italy, Reg Emilia Romagna (RER) – Italy, AAZ – Croatia, NIPHNO – Norway, AOTMiT – Poland, Osteba – Spain, AQuAS – Spain, Avalia-t – Spain, GÖG – Austria, HVB – Austria, NICE – England, UK, NHS Healthcare Improvement – Scotland, UK, HWT – Wales, UK

Synergies and Overlaps between HTA and Regulatory Requirements

Scientific Advice (Early Dialogues) on Clinical Development Plan + Design of clinical evaluations

Methodologies for Clinical Evaluation of Medical Device and IVD

PMCF/ post-market clinical evaluations (registries) and data collections

Vision (Opportunities): "seamless introduction"

- Clinical trials for both aims (CE marking and HTA)
  - Faster and less expensive innovation
  - Similar experiences with drugs ("seamless phase II/III")
- Many implications for joint work
  - Joint advice for MD manufacturers ("early dialogues")
  - Consensus on adequacy of study design
  - Consensus on post-market clinical follow-up ('PMCF', PLEG)

Aims of Workshop 1
May 29th 2018

To explore and start communication on **mutual understanding** of "environment" (requirements, methodologies, processes) between

1. **Competent Authorities** coordinated by the EU-Commission (then DG Grow) in setting up the **Medical Device Coordination Group (MDCG)**
2. **Notified Bodies** responsible for conformity assessment of MD and IVD
3. **EUnetHTA** represented by the HTA agencies regularly assessing medical devices

https://eunethta.eu/wp-content/uploads/2018/07/Workshop1_Documentation_05.07.2018.pdf

Aims of Wortshop 2
May 28th 2019

To explore **synergies** and **opportunities for exchange and collaboration** on

1. **Scientific Advice** (Early Dialogues) on Clinical Development Plan + Design of clinical evaluations
2. **Appropriate Study Designs** along the Life Cycle of Medical Devices, IDEAL-Concept, RCTs, Registries
3. **Methodological Guideline and Templates** for Clinical Evaluation of Medical Device and IVD

https://eunethta.eu/wp-content/uploads/2019/06/WS2_Documentation_25.06.2019pdf.pdf

Aims of Workshop 3
Nov 4th 2020

To explore a **dialogue** on the **evaluation of new and emerging technologies**:

Methodologies and requirements for

1. **Software** as Medical Device
2. Machine Learning **Algorithms**

Documentation: presentations and discussion: https://eunethta.eu/

I wish us all an inspiring and thought-provoking day !

Medical Devices and HTA

Anna-Eva AMPELAS

Flora GIORGIO

European Commission DG SANTE

Unit B6, Medical Device and HTA

Medical devices

Covid-19
Shortages

- Ramping up of production
- European Standards made freely available
- Combatting export restrictions
- Derogations
- Joint procurement Agreement
- Clearing House

Covid-19
main MDR regulatory measures

- Regulation (EU) 2020/561 adopted on 23 April 2020 amending MDR, as regards **the dates of application** of certain of its provisions
- Commission Implementing Regulation (EU) 2020/666 of 18 May 2020 amending Implementing Regulation (EU) No 920/2013 as regards the **renewal of designations** and the surveillance and monitoring of notified bodies

Covid-19 related guidance documents issued (selection)

- Guidance on placing medical devices and PPE **on the EU market**
- Guidance on Medical devices, Active implantable medical devices and in vitro diagnostic medical devices **in the COVID-19 context**
- Guidance to increase production of **PPE, hand gel, 3D printing**
- Guidance on regulatory requirements for **ventilators**
- Guidelines on COVID-19 IVD **tests** and their performance
- Working document on **performance of** COVID-19 **test methods**
- Database of publ. available **performance data COVID-19 IVD**
- Commission guidelines on **Union-wide derogations**
- Guidance on temporary measures on **notified body audits** during COVID-19 quarantine orders and travel restrictions + renewal designations.

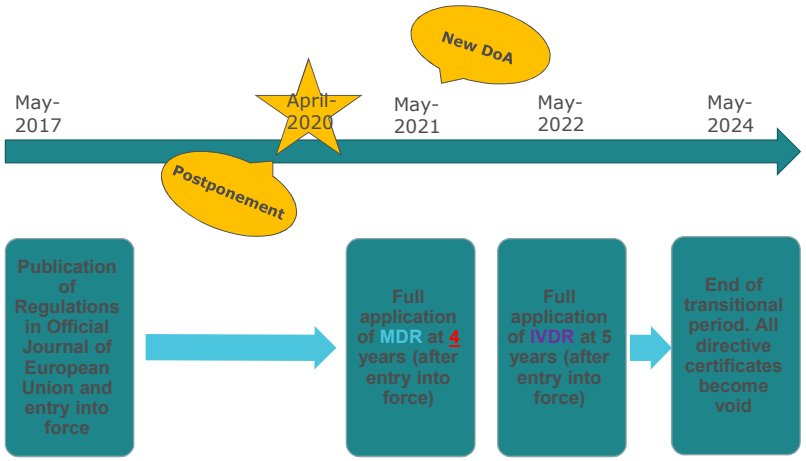
European Commission

A stronger European Health Union State of the Union Address by President Von der Leyen

- Build on first lessons from the health crisis:
- Increased funding through future proof EU4Health programme
- Strengthen crisis preparedness and management of cross-border health threats.
- As a first step, reinforce and empower EMA and ECDC
- As a second step, build a European BARDA – an agency for biomedical advanced research and development.
- Strategic stockpiling to address supply chain dependencies, notably for pharmaceutical products.
- Question of health competences (Conference on the Future of Europe).
- Learn the global lessons: Global Health Summit next year in Italy.

European Commission

MDR/IVDR Transitional period



COM implementation priorities (1)

- **Notified Bodies**
  - 62 (47+15) applications received up to date. Full scope of MDR and IVDR covered
  - 21 (17+4) notified bodies designated under new regulations
- **Governance**
  - Setting up of MDCG (November 2017)
  - MDCG technical subgroups (13) operational as from 1st Mar 2019
  - Work on 70+ guidance documents ongoing or finalised
- **Scientific structures**
  - Establishment of expert panels, expert laboratories and reference labs
  - Expert panels operational 4 q. 2020
- **Design and establishment of the new EUDAMED**
  - Core actor registration module of database to be available Q4 2020
  - Staged approach
- **Establishment of UDI system**
  - 9 guidelines published, nomenclature selected in Feb 2019, designation of issuing entities finalised in Jun 2019, release of Q/A in Aug 2019

COM implementation priorities (2)

- Mandate for revision of standards
- Communication campaign
  - Dedicated website, factsheets in all EU languages and some major non-EU languages
- Common specifications on devices without medical purpose
- Common specifications on reprocessing of single-use devices (adopted)

- Planning of activities:
- Publication of Commission's rolling plan on DG SANTE website.

COM implementation priorities (3)

Key guidance published since March 2020

March 2020

- ✓ Update of guidance on implant card
- ✓ Transitional provisions of article 120 (3) and (4) for class I medical device
- ✓ Significant changes regarding transitional provisions in Art.120
- ✓ Clinical evaluation/ Performance evaluation of medical device software

April 2020

- ✓ Update of guidance on Article 54(2)b
- ✓ PMCF templates
- ✓ Sufficient clinical evidence for legacy devices
- ✓ Clinical evaluation – Equivalence

May 2020

- ✓ Safety reporting in clinical investigations

June 2020

- ✓ Consultations of authorities on devices with ancillary substances and TSE susceptible tissues
- ✓ Update of guidance on UDI for sytems and procedure packs

July 2020

- ✓ Clinical evaluation assessment report template

August 2020

- ✓ MDCG Position Paper on the use of the EUDAMED actor registration module and of the Single Registration Number (SRN) in the Member States
- ✓ Guidance for notified bodies on the use of MDSAP audit reports under MDR and IVDR

Some critical issues

- Availability of notified bodies
- Establishment of Eudamed
- Timelines, resources and expertise

In addition:

- Covid-19
- International aspects: MRA:s (CH, AU, NZ), Customs Union Agreements (TR), UK, unilateral CE-acceptance, trade agreements

HTA

Objectives

- Promote convergence in HTA tools, procedures and methodologies
- Reduce duplication of efforts for HTA bodies and industry
- Ensure the uptake of joint outputs in Member States
- Ensure the long-term sustainability of EU cooperation

COVID crises showed the importance of EU cooperation

European Commission

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
- Stakeholders involvement
- **Independence from regulatory assessments** – create synergies

European Commission

Reminder – HTA Proposal and MD

- NO changes in MDR regulation requirements
- NO changes in market access paths for MD
- Scope of HTA regulation (some MD: class IIB and III + some IVD: class D)

One size DOES NOT fit all

Med Tech vs Pharma

- Different regulatory framework
- More fragmented market (e.g. access, products, timing)
- More heterogeneous HTA pathways
- Less developed synergies regulators - HTAs

- Specificity in developing common tools and methodologies
- Appointment of relevant Agencies with sector specific expertise
- CG and sub-groups composition: sector specific
- Develop synergies between regulators and HTAs

HTA proposal and MD

AIMS

- To provide a structure framework for relevant HTA authorities to strengthen and develop further cooperation on HTA for MD
  - Governance (Art 3);
- To develop relevant synergies between regulatory and HTA requirements
  - Governance (Art 3) + scope (Art 5)
- To produce joint work
  - Scope (Art 5) + Voluntary cooperation (Art 19)

European Commission

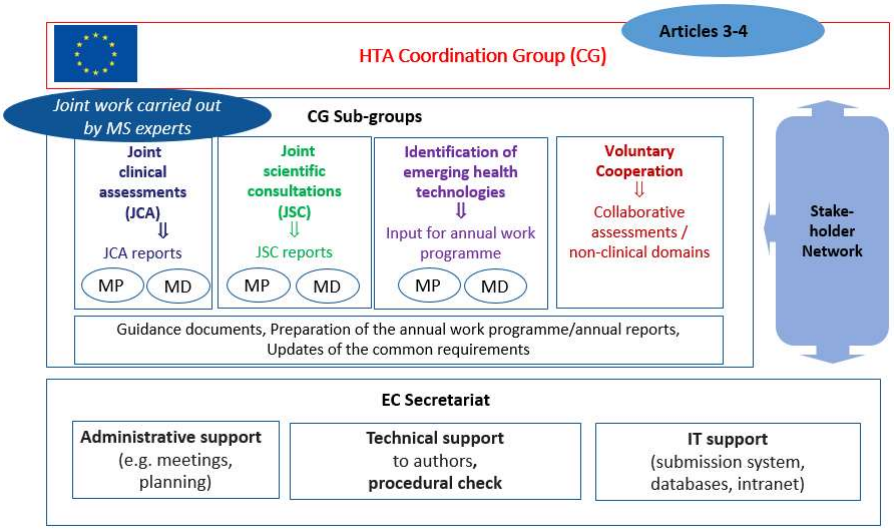
HTA Coordination Group - EC Proposal (1)

Article 3 The Member State Coordination Group on Health Technology Assessment

- MS shall designate their **national authorities and bodies responsible for HTA** as members of the Coordination Group and its sub-groups.
- MS may designate more than one authority or body responsible for HTA as members of the Coordination Group and one or more of its sub-groups -> **configurations dedicated to MP, MD**

European Commission

Governance
EU framework for cooperation - EC proposal



MP = medicinal products; MD = medical devices

HTA Coordination Group – EC Proposal (2)

Article 3 The Member State Coordination Group on Health Technology Assessment

8. The Coordination Group shall:

(a) adopt rules of procedure for the conduct of its meetings and update them where necessary;

(b) coordinate and approve the work of its sub-groups;

(c) ensure cooperation with relevant Union level bodies to facilitate additional evidence generation necessary for its work;

(d) ensure appropriate involvement of stakeholders in its work;

HTA Coordination Group – EC Proposal (3)

(e) establish sub-groups for the following:

(i) joint clinical assessments;

(ii) joint scientific consultations;

(iii) identification of emerging health technologies;

(iv) voluntary cooperation;

(v) preparation of the annual work programmes and annual reports, and updates of the common rules and working documents.

9. The Coordination Group may meet in different configurations for the following categories of health technology: medicinal products, medical devices, and other health technologies.

10. The Coordination Group may establish separate sub-groups for the following categories of health technology: medicinal products, medical devices, and other health technologies.

European Commission

HTA proposal and MD

ART 5
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) – Art 54
- **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) – Art 48

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

European Commission

HTA proposal and MD

ART 5 (cont'd)
Joint Clinical Assessments: Product scope –*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;

HTA proposal and MD

ART 19 – Voluntary cooperation

1. The Commission shall support cooperation and the exchange of scientific information among Member States on:

- (a) **non-clinical assessments on health technologies**;
- (b) **collaborative assessments on medical devices**;
- (c) health technology assessments on health technologies **other than medicinal products or medical devices;**
- (d) the provision of additional evidence necessary to support health technology assessments.

2 The Coordination Group shall be used to facilitate the cooperation referred to in paragraph 1.

[…]

HTA proposal at the Council

- HTA Proposal negotiations delayed, most recently due to COVID-19 crises
- Progress on several technical elements
- German Presidency renewed its commitment to make progress

European Commission

Thank you

European Commission

HTA proposal at the Council

Key elements:

- More “technical” elements in main text (following EP)
- Gradual implementation of full scope (step wise)
- Governance: decision making process and role of Coordination Group (e.g. producing guidance documents) vs European Commission (e.g. technical support and procedural checks)
- **Status of the JCA and commitment of MS to use it in national procedures**

European Commission

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

CIE Working Group 2020-2021 Work Programme

Updated and expected deliverables

HPRA Webinar Series on Medical Devices and in vitro diagnostic medical devices (IVDs)

13 November 11:00

Agenda

CIE WG Update

Q&A

Introduction

Devices are different to Medicinal Products

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

Slide 43

Drugs and devices – snapshot of important differences

	Medicinal products	Medical devices
Standard clinical development phases	Highly standardised (phase I, II, III)	Less standardised Product dependent
Clinical study design	Highly standardized Double-blind RCT	Less standardised
Irreversible effects on study subjects	Rare	Common particulary with permanent implants
Types of organisations who engage in product development	Mostly large and established	Variable, from large to small / start-ups

Slide 44

MDR 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

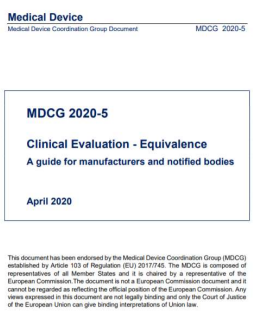
CIE Working Group Guidance

Reference	Title	Publication
MDCG 2020-13 - Word version	Clinical evaluation assessment report template	July 2020
MDCG 2020-10/1 MDCG 2020-10/2	Guidance on safety reporting in clinical investigations Appendix: Clinical investigation summary safety report form	May 2020 May 2020
MDCG 2020-8	Guidance on PMCF evaluation report template	April 2020
MDCG 2020-7	Guidance on PMCF plan template	April 2020
MDCG 2020-6	Guidance on sufficient clinical evidence for legacy devices	April 2020
MDCG 2020-5	Guidance on clinical evaluation – Equivalence	April 2020
MDCG 2019-9	Summary of safety and clinical performance	August 2019

Slide 46

MDCG Clinical Guidance for Legacy Products

What are we talking about?



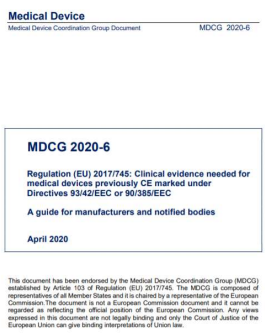
Medical Device
Medical Device Coordination Group Document MDCG 2020-5

MDCG 2020-5

Clinical Evaluation - Equivalence
A guide for manufacturers and notified bodies

April 2020

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



Medical Device
Medical Device Coordination Group Document MDCG 2020-6

MDCG 2020-6

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

A guide for manufacturers and notified bodies

April 2020

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Slide 48

What is the scope?

Legacy devices, i.e. devices previously CE marked under the MDD or AIMDD

Additional definitions and descriptions

- Well established technology
- Scientific validity
- Level of clinical evidence
- Similar device

What is the purpose?

Guidance for manufacturers and notified bodies to prepare for the conformity assessment procedure according to the MDR

With respect to equivalence – a **gap analysis** and **table** is provided for assessing legacy products with respect to equivalence requirements in MDR

What is <u>not</u> covered?

Not comprehensive methodology for all products

Not a complete guide for clinical evaluation

Not a guide to the 'contract' requirements relating to equivalence for high risk products

What is covered?

MDCG-6 shows **important changes** that should be taken into account for clinical evaluation for MDR

MDCG-6 cites the **aspects from MEDDEV** guidance, which legacy MFRs may utilise to support MDR conformity, for example aspects of 2.7/1Rev. 4 or 2/12.2

Stepwise approach to preparing a **clinical evaluation plan** for MDR

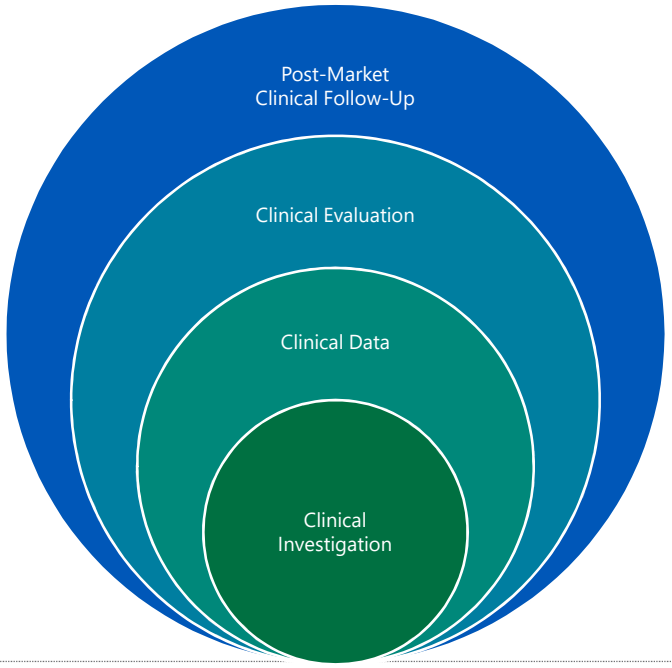
Conclusion

Take home message

For legacy products, there is **no automatic presumption of conformity**, i.e. no grandfathering

Plan for compliance with MDR requirements relating to **clinical evaluation and PMCF**

Remember that the **key concepts** of clinical evaluation remain, however there are also a range of **new requirements**, **processes** and **conclusions**, especially for high risk devices



HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Thank you

Contact: devices@hpra.ie

Status quo of Implementation of the MDR/IVDR from the Perspective of Notified Bodies

F. Schlemmer, Team-NB Director
November 4th 2020 – on line
2nd workshop of the EUnetHTA Task Force on HTA and MDR

EUnetHTA-20201104

Team-NB

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

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**

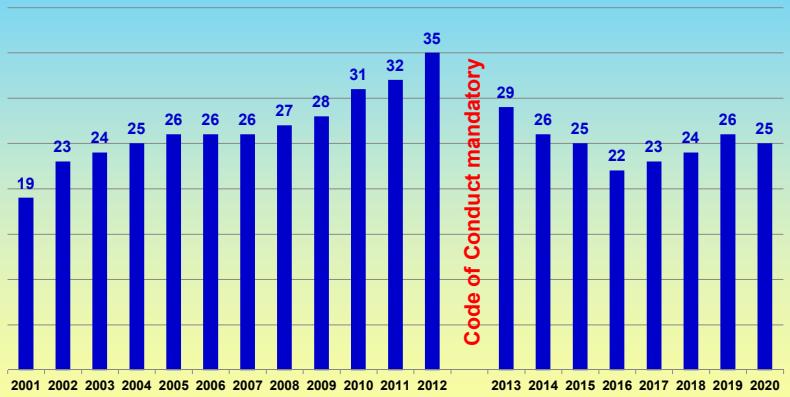
New regulations: NB-Med ⇨ NBCG

- **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, especially on procedural and practical impact.
  - Drafts reports on ethical aspects of the activities of NBs.
  - Ensures consistency with standardisation work at European level.

New regulations: NB-Med ⇨ NBCG

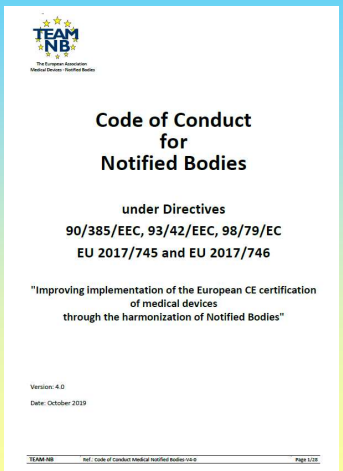
- **NBCG:**
  - Co-chair : Sabina Hoekstra-van den Bosch
  - Co-chair : Suzanne Halliday
  - Secretary: Tom Patten
- **NBTG - MD:**
  - Chair: Thomas Feldmann
- **NBTG - IVD:**
  - Chair: Marta Carnielli

Team-NB : Members



Team-NB : Code of Conduct

- **Mandatory to sign for TEAM-NB members**
- **Version 4.0 approved on October 2019**
- **Alignment with MDR / IVDR requirements**
- **Available on website www.team-nb.org**



Code of Conduct
for
Notified Bodies

under Directives
90/385/EEC, 93/42/EEC, 98/79/EC
EU 2017/745 and EU 2017/746

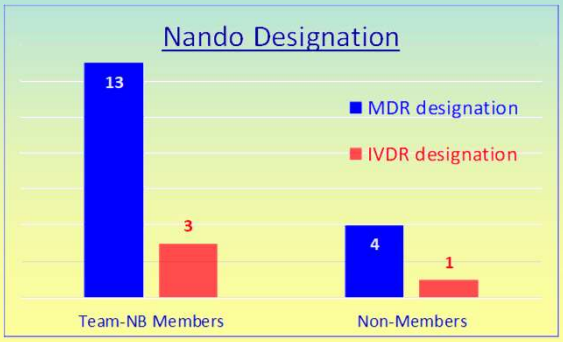
"Improving implementation of the European CE certification of medical devices
through the harmonization of Notified Bodies"

Version: 4.0

Date: October 2019

Implementation of the new regulations

- **Team-NB established working groups from 2016**
  - ⇨ **Aims**
    - Help members to be designated
    - Allow harmonization



Implementation of the new regulations

- **MDCG mirror WGs**
  - ⇨ **Aims**
    - to allow notified bodies members to speak of 1 voice
    - to prepare and participate in the MDCG meetings
    - to write reports
      - distributed to all members
      - to share information
    - to comment on MDCG proposals
    - to write Position Papers (published on Team-NB web site)

Implementation of the new regulations

❖ Task Forces

⇨ Aims

- to address specific topics of NBs interest
  - Article 117
  - TCP III - Taiwan
  - Transfer Agreement
  - Standard fees publically available
  - TOC (table of content)

- to write Position Papers (published on Team-NB web site)

Implementation of the new regulations

❖ Trainings

⇨ Aims

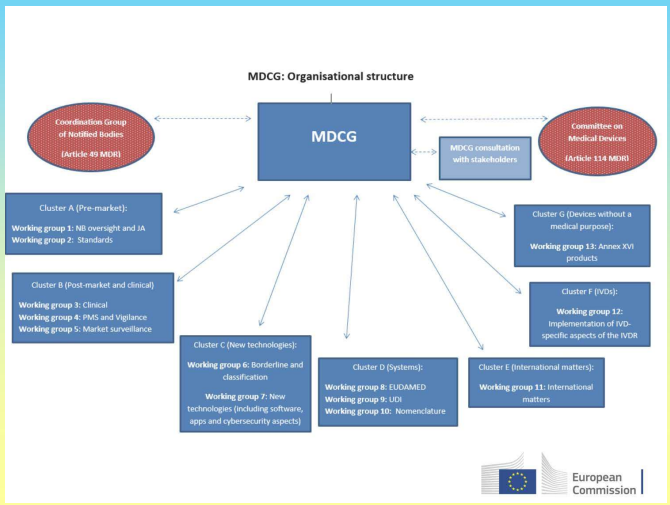
- to help NBs to deal with new MDR / IVDR requirements in their assessment.
- to achieve a better harmonisation among NBs thanks to the exchanges

Implementation of the new regulations

- **Trainings in 2019**
  - Clinical data: 3 sessions
- **Trainings in 2020**
  - Clinical data: 1 session
  - Technical Documentation: 2 sessions in September + 1 Q4
  - Risk Management: 2 sessions in December
- **Trainings in 2021**
  - Performance for in vitro diagnostics
  - Software classification

Implementation of the new regulations

- **Participation as observers to the MDCG sub-groups**



New regulations : 7 important changes

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

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 important and more detailed in new regulation**

Clinical Data

- **MDR:**
  - **Clinical aspects have been significantly increased**

    "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."

Clinical Data

- **Clinical data definition**
  - information concerning safety or performance that is generated from the use of a device and is sourced from the following:
    - **clinical investigation(s)** of the device concerned
    - clinical investigation(s) or other studies reported in scientific literature, of a device for which **equivalence** to the device in question can be demonstrated
    - reports **published in peer reviewed scientific literature** on other clinical experience of either the **device in question** or a device for which **equivalence** to the device in question can be demonstrated
    - clinically relevant information coming from **post-market surveillance**, in particular the **post-market clinical follow-up**

Clinical Data

- **Equivalence approach**
  - Technical, Biological and Clinical 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 access to the data on devices to which Manufacturer is claiming equivalence
  - Results in CER , which is part of the TD

Post Market surveillance

- New requirements to keep PMS - data as part of the Technical Documentation

Periodic Safety Update Report (PSUR)

- Manufacturer shall prepare a periodic safety update report summarizing the results and conclusions of the analyses of the gathered post-market surveillance data - together with a rationale and description of any preventive and corrective actions taken

  (except class I, PMS only)

Clinical Evaluation - Duties of the NB

- **Examine, validate and verify that manufacturers' procedures and documentation adequately address:**
  - planning, conduct, assessment, reporting and updating of the clinical evaluation
  - PMS and PMCF
  - interface with the risk management process,
  - appraisal and analysis of the available data and its relevance with regard to demonstrating conformity with the relevant requirements, and
  - the conclusions drawn with regard to the clinical evidence and drawing up of the clinical evaluation report.

Clinical Evaluation - Duties of the NB

- **The notified body's assessment of clinical evaluations shall cover:**
  - intended use specified by the manufacturer and claims for the device defined by it,
  - planning of the clinical evaluation,
  - methodology for the literature search,
  - relevant documentation from the literature search,
  - clinical investigation,

To be followed

Clinical Evaluation - Duties of the NB

- **The notified body's assessment of clinical evaluations shall cover:**

Follow up…

- 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 post-market surveillance and PMCF,
- the clinical evaluation report, and
- justifications in relation to non-performance of clinical investigations or PMCF.

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Members :

EUnetHTA Task Force on HTA and Medical Devices

A deep dive on Medical Device Software

4 November 2020

Nada Alkhayat
Policy Officer
Unit B.6: Medical Devices, Health Technology Assessment
Directorate-General for Health and Food Safety (DG SANTE)

1. A new EU Regulatory system for Medical Devices

EU legislation on medical devices

- **Current Directives and new Regulations**:
  - Directive 90/385/EEC on active implantable medical devices (AIMDD)
  - Directive 93/42/EEC on medical devices (MDD)
  - **Regulation (EU) 2017/745 on medical devices (MDR)** adopted in April 2017 and entered into force in May 2017, as amended – fully applicable from **26 May 2021**
  - Directive 98/79/EC on *in vitro* diagnostic medical devices (IVDMDD)
  - **Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR)** adopted in April 2017 and entered into force in May 2017, as amended – fully applicable from **26 May 2022**
- **Specific transitional provisions** (Articles 120 MDR and 110 IVDR)

Regulation (EU) 202/561 and main consequences

- Regulation (EU) 2020/561 adopted on 23 April 2020 **amending MDR**, as regards the **dates of application** of certain of its provisions
- Commission Implementing Regulation (EU) 2020/666 of 18 May 2020 amending Implementing Regulation (EU) No 920/2013 as regards the renewal of **designations** and the **surveillance and monitoring of notified bodies**
- Commission Recommendation (EU) 2020/403 of 13 March 2020 on **conformity assessment and market surveillance** procedures within the context of the COVID-19 threat

Pillars of the EU regulatory framework for devices (MD/IVD)

- The "New Approach" and the "**New Legislative Framework"** (Regulation (EC) 765/2008, Decision 768/2008/EC, and others)
- **Specific scope and definitions,** roles and responsibilities of economic operators and of national competent authorities
- **Essential requirements** (health, safety and performance) supported by voluntary harmonised European **standards**
- **Classification and conformity assessment** procedures according to risks, with third party conformity assessment bodies ("notified bodies") and related certificates for medium- and high-risk devices

Objectives of the new EU legislation on medical devices

- establish a **modernised** and more **robust, transparent** and **sustainable** EU regulatory framework on medical devices, while ensuring **free and fair trade** of devices throughout the EU internal market
- keep up with **advances in science and technology** whilst **supporting innovation** ensure a better and consistently
- **high level of health and safety protection of public health** and patient safety for citizens using medical devices in Europe.

MDR/IVDR MDCG guidance specific to software

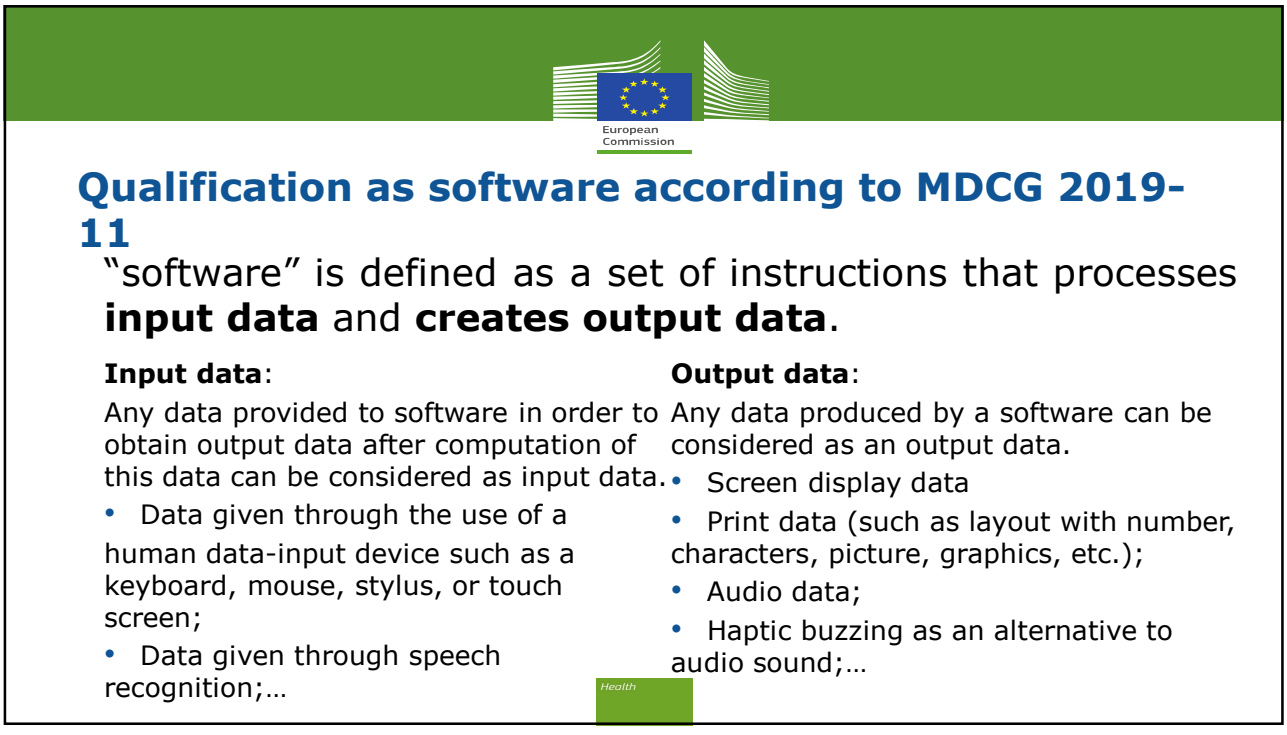
Health

MDCG guidance specific to software under MDR and IVDR

Reference	Title	Publication
MDCG 2019-11	Qualification and classification of software - Regulation (EU) 2017/745 and Regulation (EU) 2017/746	October 2019
MDCG 2019-16	Guidance on cybersecurity for medical devices	December 2019
MDCG 2020-1	Guidance on clinical evaluation (MDR) / Performance evaluation (IVDR) of medical device software	March 2020

Health


European Commission
Medical Device
Medical Device Coordination Group Document
MDCG 2019-11
MDCG 2019-11
Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR
October 2019
Health


European Commission
Qualification as software according to MDCG 2019-11
"software" is defined as a set of instructions that processes **input data** and **creates output data**.
Input data:
Any data provided to software in order to obtain output data after computation of this data can be considered as input data.
• Data given through the use of a human data-input device such as a keyboard, mouse, stylus, or touch screen;
• Data given through speech recognition;…
Output data:
Any data produced by a software can be considered as an output data.
• Screen display data
• Print data (such as layout with number, characters, picture, graphics, etc.);
• Audio data;
• Haptic buzzing as an alternative to audio sound;…
Health

Qualification as driving or influencing software

Is software **intended to drive or influence** the use of **a (hardware)** medical device and ***does not*** **have** or **perform a medical purpose *on its own*, *nor* does it create information *on its own*** for one or more of the medical purposes described in the definition of a medical device or an *in vitro* diagnostic medical device. This software can, but is not limited to:

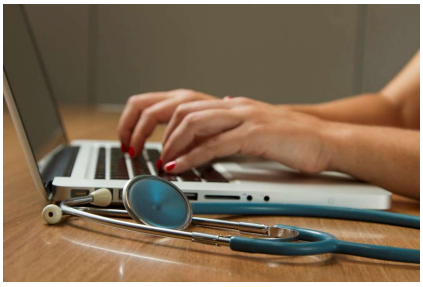
a) operate, modify the state of, or control the device either through an interface (e.g., software, hardware) or via the operator of this device

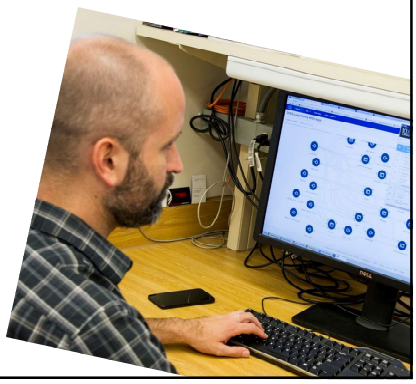
b) or supply output related to the (hardware) functioning of that device

Note: Software that is driving or influencing the use of a medical device is covered by the medical devices regulations either as a part/component of a device or as an accessory for a medical device.

Qualification as MDSW

Medical device software is software that **is intended** to be used, **alone or in combination**, for a purpose as specified in the definition of a "**medical device**" in the MDR or IVDR, regardless of whether the software is **independent** or **driving or influencing** the use of a device.





Key questions to ask

- Intention?
- Accessory, Annex XVI or driving or influencing software?
- Is it performing more than storage, archival, communication or simple search?
- If so, is the action for the benefit of individual patients?
- Meets the definition of a MDSW?

Key questions to ask - Part 2

- IVD?
- Is the data obtained solely by IVD MDs?
- If not, is the intended purpose substantially driven by IVD data?

Classification

Implementing rules 3.3 and 3.5 – special consideration:

- 'If software is independent of any other device, it shall be classified in its own right'

- 'If several rules, or if, within the same rule, several sub-rules, apply to the same device based on the device's intended purpose, the strictest rule and sub-rule resulting in higher classification will apply'

Classification

- As software is defined as an active device, for the classification of active (hardware) devices, which also includes MDSW providing information for patient management, Rules 9, 10, 11, 12, 13, 15 and 22 of Annex VIII MDR 2017/745 should be considered.

- In line with implementation rule 3.5, the strictest rule or sub-rule should hence apply. MDSW should be classified in the same way, regardless of the software's location or the type of interconnection between the software and a (hardware) device.

European Commission

Classification – Rule 11 and IMDRF risk categorisation

		Significance of Information provided by the MDSW to a healthcare situation related to diagnosis/therapy		
State of Healthcare situation or patient condition		High Treat or diagnose ~ IMDRF 5.1.1	Medium Drives clinical management ~ IMDRF 5.1.2	Low Informs clinical management (everything else)
	Critical situation or patient condition ~ IMDRF 5.2.1	Class III Category IV.i	Class IIb Category III.i	Class IIa Category II.i
	Serious situation or patient condition ~ IMDRF 5.2.2	Class IIb Category III.ii	Class IIa Category II.ii	Class IIa Category I.ii
	Non-serious situation or patient condition (everything else)	Class IIa Category II.iii	Class IIa Category I.iii	Class IIa Category I.i

Health

European Commission

Medical Device

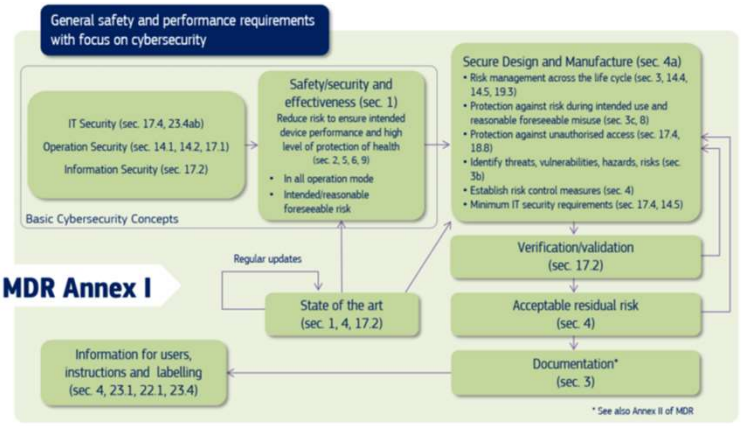
Medical Device Coordination Group Document MDCG 2019-16

MDCG 2019-16
Guidance on Cybersecurity for medical devices

December 2019

Health

Guidance on cybersecurity for medical devices – MDCG 2019-16



Guidance on cybersecurity for medical devices – MDCG 2019-16

Main topic	Section number MDR Annex I	Section number IVDR Annex I
Device performance	1	1
Risk reduction	2	2
Risk management system	3	3
Risk control measures	4	4
Minimisation of foreseeable risks, and any undesirable side-effects	8	8
Combination/connection of devices/systems	14.1	13.1
Interaction between software and the IT environment	14.2.d	13.2.d
Interoperability and compatibility with other devices or products	14.5	13.5
Repeatability, reliability and performance	17.1	16.1
Development and manufacture in accordance with the state of the art taking into account the principles of development life cycle, risk management, including information security, verification and validation	17.2	16.2
Minimum IT requirements	17.4	16.4
Unauthorised access	18.8	-
Lay persons	22.1	-
Residual risks (information supplied by the manufacturer)	23.1 g	20.1 g
Warnings or precautions (information on the label)	23.2 m	20.2 m
Residual risks, contra-indications and any undesirable side-effects, (information in the instructions for use)	23.4 g	-
Minimum IT requirements (information in the instructions for use)	23.4.ab	20.4.1.ah

European Commission

Guidance on cybersecurity for medical devices – MDCG 2019-16 – a lifecycle approach

Pre-market activities	Post-market activities
Secure Design (Annex I)	
Risk management (Annex I)	Risk management (Annex I)
Establish Risk Control Measures (Annex I)	Modify Risk Control Measures /Corrective Actions/Patches (Annex I)
Validation, Verification, Risk Assessment, Benefit Risk Analysis (Annex I)	Validation, Verification, Risk Assessment, Benefit Risk Analysis (Annex I)
Technical Documentation (Annex II and III)	Maintain and update a Post-market Surveillance Plan and Post-market Surveillance System (Article 83 and 84)
Conformity Assessment (Article 52)	Trend Reporting (Article 88)
Establish a Post-market Surveillance Plan and Post-market Surveillance System (Article 83 and 84)	Analysis of Serious Incidents (Article 89)
Clinical evaluation process (Chapter VI)	Post-Market Surveillance Report (Article 85)
	Periodic Safety Update Report (Article 86)
	Update Technical Documentation (Annex II and III)
	Inform the Electronic System On Vigilance (Article 92)

European Commission

Medical Device
Medical Device Coordination Group Document MDCG 2020-1

MDCG 2020-1

Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software

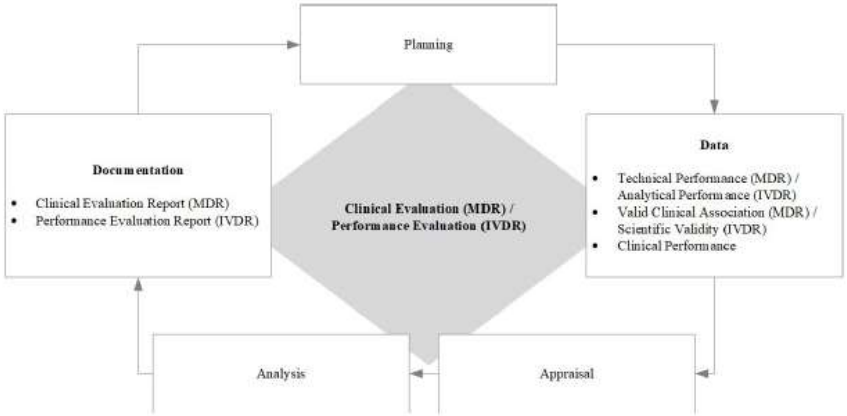
March 2020

Health

Different MDSW and how Clinical/Performance Evaluation should be conducted

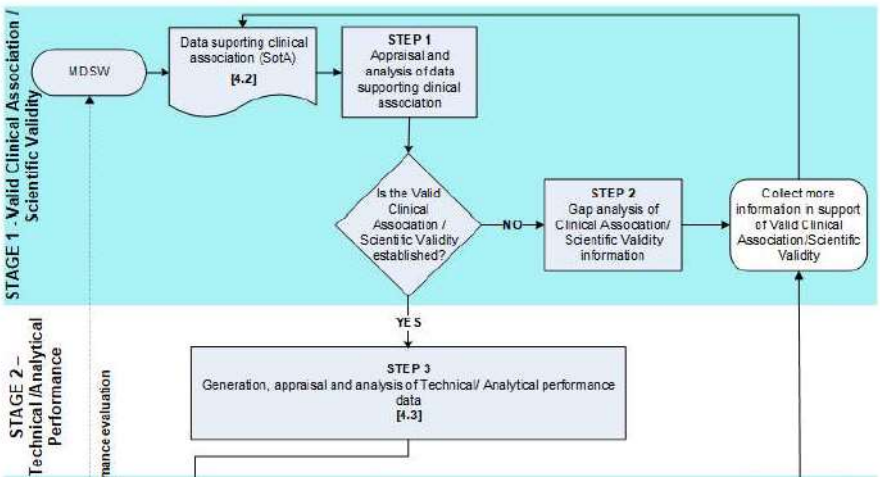
Model of Software	CLINICAL EVALUATION (MDR) / PERFORMANCE EVALUATION (IVDR) - scope
MDSW (with independent intended purpose and claimed CLINICAL BENEFIT)	MDSW only
MDSW (with intended purpose and claimed CLINICAL BENEFIT related to driving or influencing a medical device for a medical purpose)	MDSW and the driven or influenced medical device Notes 1,2
Software driving or influencing the use of a medical device (with no independent intended purpose or independent claimed CLINICAL BENEFIT)	Driven or influenced medical device including the software (component or accessory)

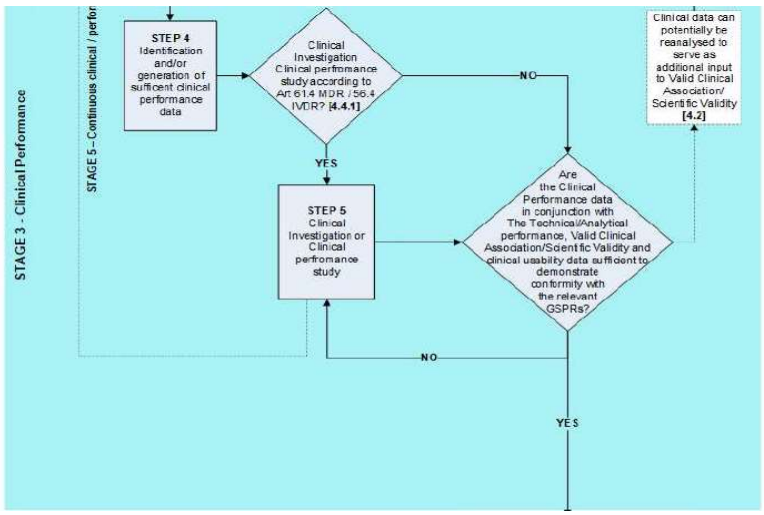
Overview on Clinical Evaluation/Performance Evaluation of MDSW



Pillars of Clinical Evaluation/Performance Evaluation

- Valid clinical association/Scientific validity
- Technical performance/Analytical performance
- Clinical Performance





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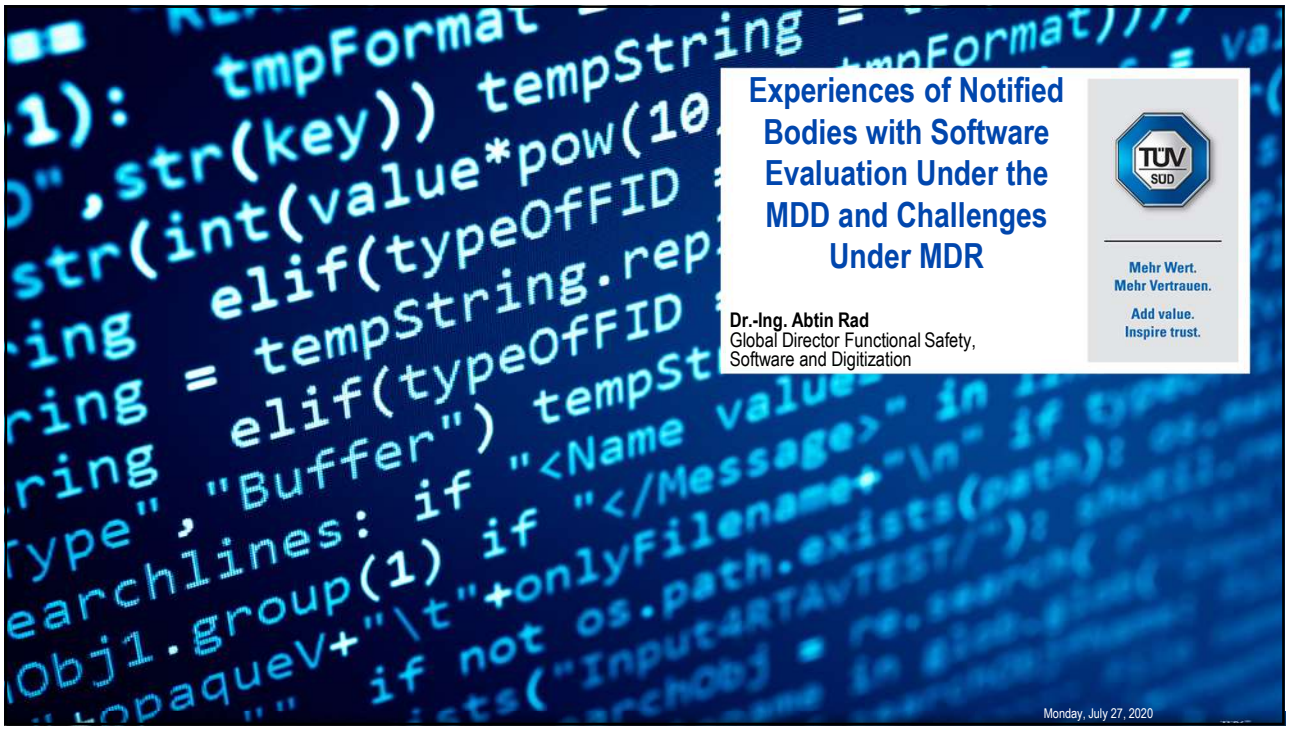

Table of content

1. Software and medical device directive
2. Software and medical device regulations
3. Challenges of MDR
   a. Cybersecurity
   b. Data privacy
   c. Artificial Intelligence

Software and **medical device directive** (93/42/EEC)

- **Medical device:** "… *any instrument … including the* ***software****…*" [MDD 93/42/EEC]
- **Annex I** of the directive defines **Essential Requirements (ER)**
  - **ER 2**: …*devices must conform to safety principles, taking account of the generally acknowledged* ***state of the art***
  - **ER 10**: … ***measurements*** *must be displayed or compared to a* ***legal unit*** *(80/181/EEC)*
  - **ER 12.1**: Devices incorporating **electronic programmable systems** must … ensure … **repeatability, reliability and performance**…
- **Compliance** to ER is **presumed** if **harmonized standard** used by manufacturer

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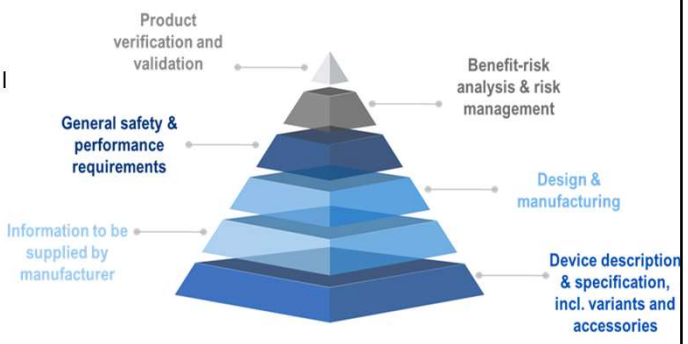
Software and **medical device regulations** – Conformity assessment

1. Set up a **quality management system**
   "…shall ***establish****, … implement a* ***quality management system*** *… "* [MDR Annex II]

2. Certify your quality management system
   "The ***notified body*** *shall* ***audit*** *the quality management system …"* [MDR Annex II]

3. **Technical documentation according** to Annex II
   "… *The* ***technical documentation*** *…* ***drawn*** *up by the* ***manufacturer*** *… be presented in a … ,* ***organised****, readily* ***searchable*** *… "* [Annex II MDR]



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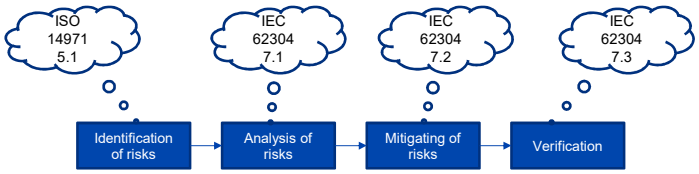
Software and **medical device regulations – Challenges**

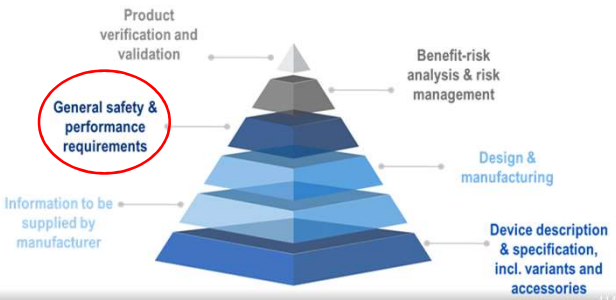
Assessment according to MDD

a. Intended use, **qualification** and classification
b. Technical description and **specification**
c. Compliance to the **Essential Requirements**
d. Risk Management
e. Assessment of preclinical data
f. Clinical evaluation
g. Declaration of conformity
h. Instruction for use …



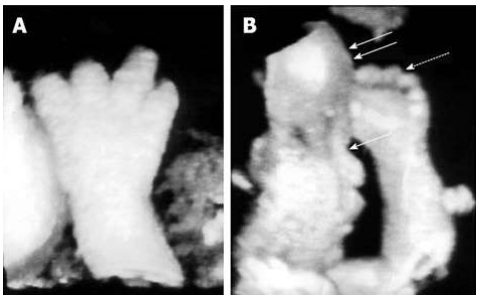
Software and **medical device regulations – Challenges**

- **Software life cycle**
  - *"Software … that is intended to be used … with **mobile computing platforms**.. taking into account the specific features of the mobile platform"*
- **Cybersecurity:**
  - *"… the software shall be **developed** … taking into account … **information security** …"* [MDR Annex I, **17.2**]
  - "… **requirements** concerning … **IT security measures**, … **unauthorised access**" [MDR Annex I, **17.4**]
- **Functional safety**
  *"…In … a **single fault condition**, appropriate **means** shall … **eliminate** … **risks** or **impairment** of **performance**"*
  [MDR Annex I, **17.1**]
- **Software life cycle**
  *"… software shall be developed … taking into account **development life cycle**…"* [MDR Annex I, **17.2**]



Software and **medical device regulations – Challenges**

- **State of the art**
  - *Devices … shall be safe …. taking into account the **generally acknowledged state of the art*** [MDR GSPR 1]
  - *Risk control measures adopted by manufacturers … shall conform to safety principles, taking account of the **generally acknowledged state of the art*** [MDR GSPR 4]
- **New technologies such as artificial intelligence (AI)**
  - Explainability of AI
  - Quality of data
  - Security and stability of AI



Renna MD, Pisani P, Conversano F, et al. Sonographic markers for early diagnosis of fetal malformations. World Journal of Radiology. 2013 Oct;5(10)

Mehr Wert.
Mehr Vertrauen.
Add value.
Inspire trust.

Thank you for your attention

Dr.-Ing. Abtin Rad
Global Director Functional Safety, Software and Digitization

Phone: +49 (0)89 5008-4388
E-Mail: abtin.rad@tuvsud.com

NICE National Institute for Health and Care Excellence

Building an HTA framework to evaluate digital health technologies

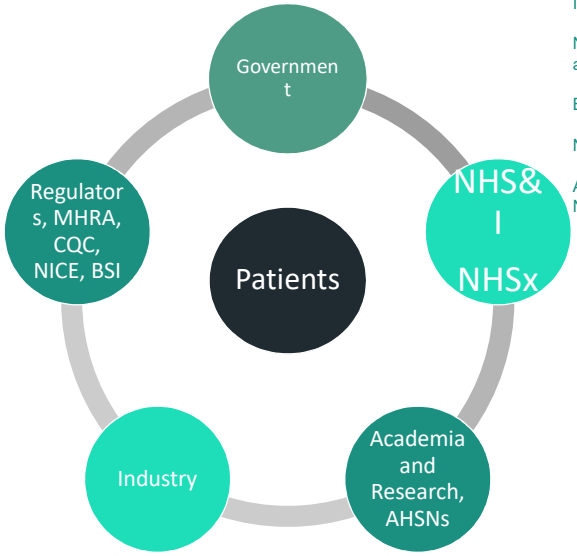
NICE

Joanne.holden@nice.org.uk

Outline

- Many interests
- The challenge
- Basis for a framework: the Evidence Standards Framework
- Testing a framework: the NICE Digital Health Technology Pilot

Many interests in digital health technologies (DHT)



MHRA: Medicines and Healthcare products Regulatory Agency

CQC: Care Quality Commission

NHSE/I: NHS England and NHS Improvement

NICE: National Institute for Health and Care Excellence

BSI: British Standards Institute

NHS: National Health Service

AHSNs: Academic Health Science Networks

NICE

The Challenge

- Companies/sponsors are not clear what evidence they need to produce
- Commissioners are unclear what they are looking for
- A cycle of pilots and trials in the innovation space with little at scale implementation of such tools – waste of time and resources
- Whole system process – where do all the system stakeholders fit in and in what order?

NICE

Evidence Standards Framework

Evidence standards framework for digital health technologies

As digital health technologies develop at an increasing pace, we've worked with partners to develop standards that ensure new technologies are clinically effective and offer economic value.

The aim of these standards is to make it easier for innovators and commissioners to understand what good levels of evidence for digital healthcare technologies look like, while meeting the needs of the health and care system, patients, and users.

We've created these standards as part of a working group led by NHS England. The group also includes:

- Public Health England
- MedCity
- DigitalHealth.London.

NICE National Institute for Health and Care Excellence

NHS England

Public Health England

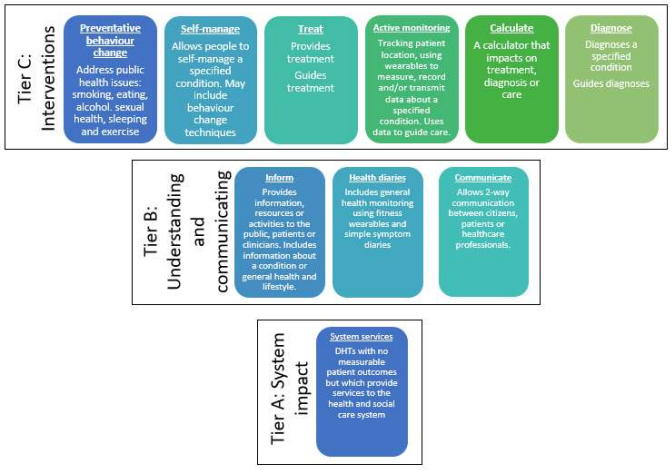
MEDCITY CAMBRIDGE | LONDON | OXFORD

DigitalHealth.London

Evidence Standards Framework - concept

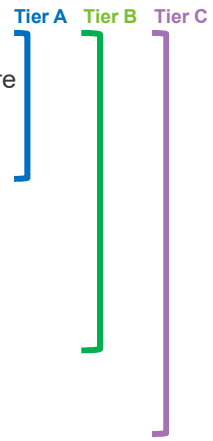
1. Define functional classification – what does the DHT do?
2. Functional classification determines evidence requirements (types of evidence)
3. Contextual questions determine what depth of evidence is required (standards of evidence)

DHTs are classified by function and stratified into evidence tiers



Standards cover multiple types of evidence

- Credibility with UK health and social care professionals
- Relevance to current care pathways in the UK health and social care system
- Acceptability with users
- Equalities considerations
- Accurate and reliable measurements (if relevant)
- Accurate and reliable transmission of data (if relevant)
- Reliable information content
- Ongoing data collection to show usage of the DHT
- Ongoing data collection to show value of the DHT
- Quality and safeguarding
- Demonstrating effectiveness
- Use of appropriate behaviour change techniques (if relevant)



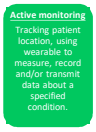
Defining type and quality of evidence: Tier C (intervention) evidence standards

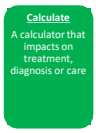
Treat, Active Monitoring, Calculate, Diagnose:

- Minimum evidence standard:
  High quality observational or quasi-experimental studies demonstrating relevant outcomes. Comparative
- Best practice standard:
  High quality intervention study (quasi-experimental or experimental design). Comparative

Preventative behaviour change, Self-manage:

- Minimum evidence standard:
  High quality intervention study (experimental or quasi-experimental design) showing improvements in relevant outcomes
- Best practice standard:
  High quality randomised controlled study - relevant setting to UK. Comparative. Demonstrating consistent benefit including clinical outcomes in target population





NICE

Contextual questions (level of evidence)

Question	Answer	Risk	Description and risk adjustment
Are the intended users of this DHT considered to be in a potentially vulnerable group such as children or at-risk adults?	Yes	**Higher**	NHS England defines at-risk adults as adults: 'who may be in need of community care services by reason of mental or other disability, age or illness; and who is or may be unable to take care of him or herself, or unable to protect him or herself against significant harm or exploitation.' If the DHT is intended used by people considered to be vulnerable then a commissioner may consider whether a higher level of evidence is needed, and/or some relevant expert opinion on whether the needs of the users are being appropriately addressed.
	No	Lower	
How serious could the consequences be to the user, if the DHT failed to perform as described?	Immediate risk of death or serious harm	Higher	A higher level of potential harm may indicate that the best practice evidence level should be used.
	Short term worsening of condition or delayed diagnosis	Higher	
	Loss of emergency alerting systems	Higher	
	No immediate risk of harm	Lower	
	No risks	Lower	

NICE

Contextual questions continued

Is the DHT intended to be used with regular support from a suitably qualified and experienced health or social care professional?	**Yes**	**Lower**	DHTs that are intended to be used with support (that is, with regular support or guidance from a suitably qualified health or social care professional) could be considered to have lower risk than DHTs that are intended to be used by the citizen/patient on their own. (*Use with caution depending on DHT an context as the involvement of a health professional could in itself present a specific risk)*
	No	Higher	
Does the DHT include machine learning algorithms or artificial intelligence?	**Yes**	**Higher**	Refer to the Code of Conduct for Data Driven Health and Care Technology to understand any additional considerations when evaluating DHTs that use AI or machine learning.
	No	Lower	
Is the financial or organisational risk of the DHT expected to be very high?	**Yes**	**Higher economic risk**	DHTs with very high financial risk should be assessed using the best practice standards to provide surety that the DHT represents good value. High organisational risks may include situations in which implementing the DHT would need complex changes n working practices or care pathways.
	No	Lower economic risk	Lower evidence standards

NICE

Resources available

User guide

Functional classification examples

Glossary

Budget impact tool

BI/CCA guide

Effectiveness and economic evidence case studies

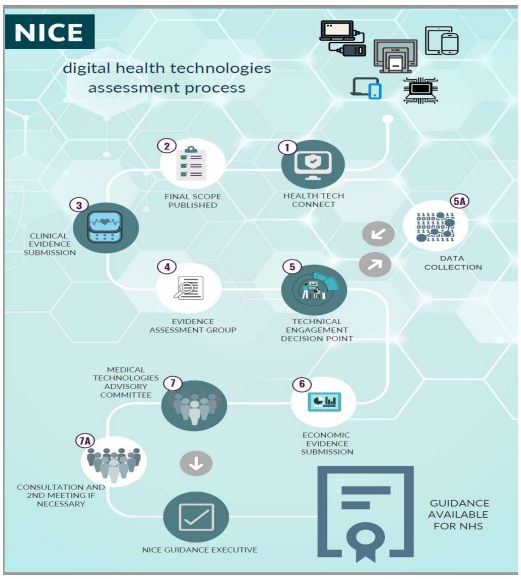
https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies

NICE

NICE Digital Health Technologies (DHT) Pilot

- Followed the success of the ESF
- Commissioned by NHS England and Improvement
- Test whether existing methods are appropriate
- Understand the assurance infrastructure for DHTs
- 5 DHTs, 1 went to guidance development
- Valuable lessons learned

NICE



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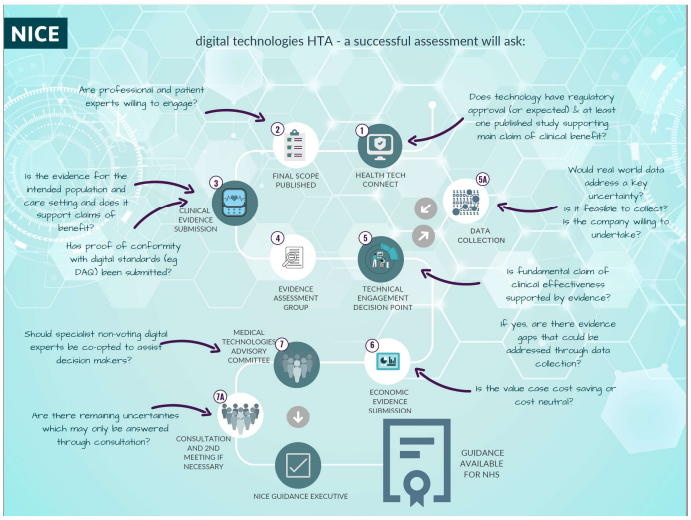

A successful digital health technology assessment framework will:

- Establish strong links with all parts of the regulatory, commissioning, strategic, academic (etc) infrastructure
- Set expectations of evidence requirements – type, quantity, quality
- Offer lots of interaction with technology sponsor/developer
- Consider data collection needs at a very early stage
- Respond to expectations for faster, streamlined process for DHTs
- For the future: become digital?

eunethta

Workshop on MDR
4 November 2020

Machine learning algorithms in cardiology – evaluation needs and challenges from the perspective of the clinician

Alan G Fraser

Department of Cardiology, University Hospital of Wales, and Cardiff University

Cardiovascular Imaging & Dynamics, Katholieke Universiteit Leuven

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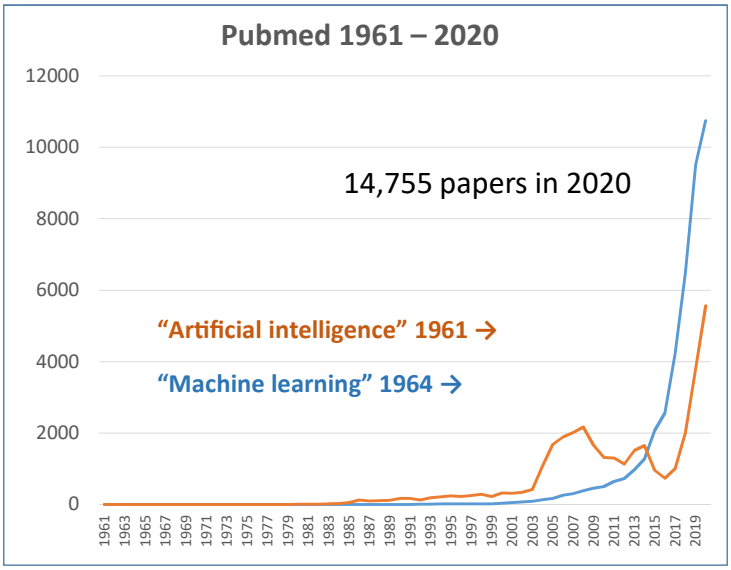
Artificial intelligence and machine learning in medicine are fashionable



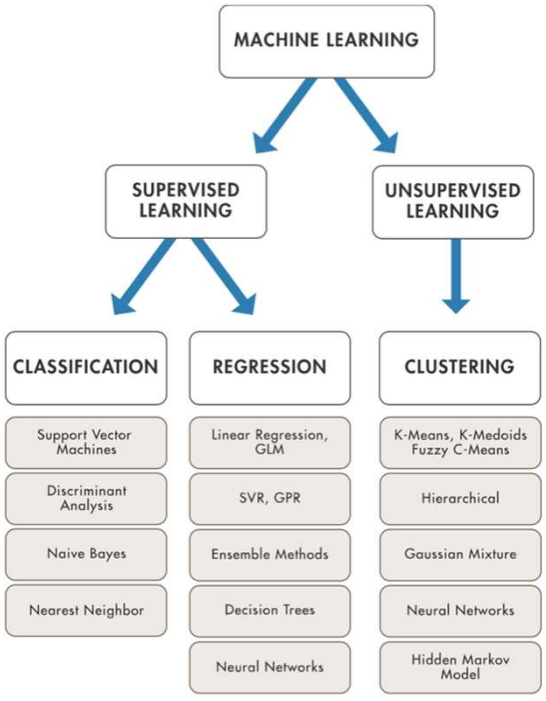
- A necessary development to analyse big datasets
- Computers use but don't "understand" binary code
- (Health) risks possible from incomplete understanding or inappropriate application
- No machine learning algorithm or neural network will perform perfectly
- Role should be to ***support not replace*** clinical judgement

EU Ethics Guidelines for Trustworthy Artificial Intelligence

1. Human agency and oversight
2. Technical robustness and safety
3. Privacy and Data governance
4. Transparency
5. Diversity, non-discrimination and fairness
6. Societal and environmental well-being
7. Accountability

"Doctors can potentially perform a more accurate and detailed analysis of a patient's complex health data, even before people get sick .. leading to earlier detection of diseases, more efficient development of medicines, more targeted treatments and ultimately more lives saved"

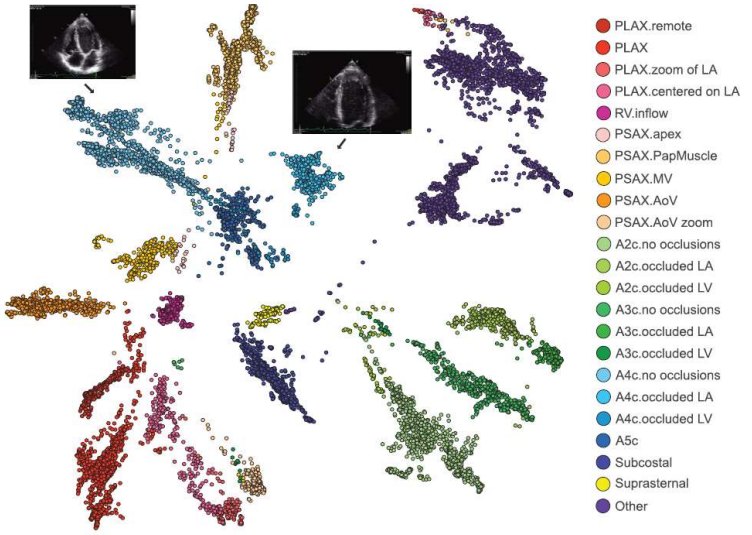
https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai



Applications of machine learning in cardiology

- Acquisition of images
- Segmentation & measurement
- Pathophysiological exploration
- Diagnosis
- Prognosis
- Clinical decision support
- Managing probabilities

Fully automated interpretation of echocardiogram in clinical practice

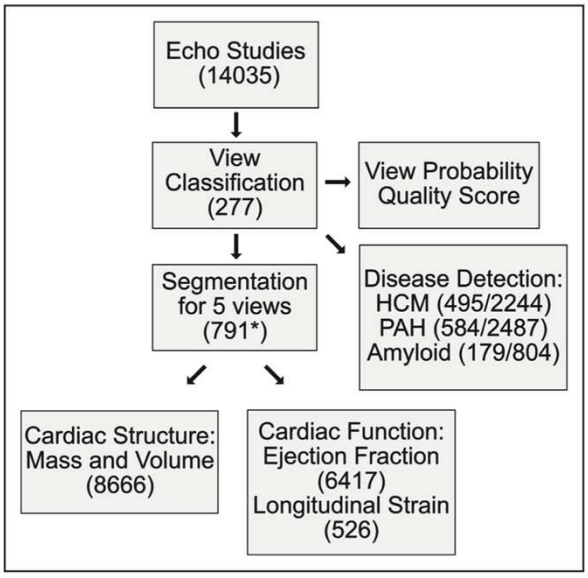


t-Distributed Stochastic Neighbor Embedding (t-SNE) visualization of view classification

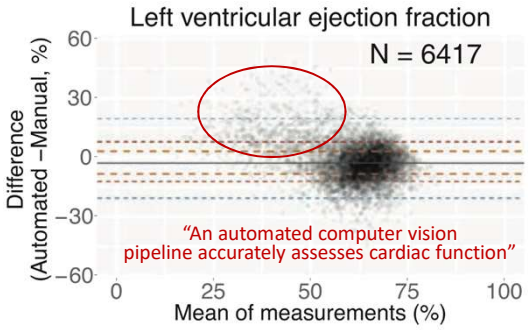
View	Number of Images Used for Training	Segmented Area	IoU Accuracy
A2c	214	Left atrium blood pool	88.2
		Left ventricle blood pool	89.1
		Left ventricle myocardium	72.2
A3c	141	Left atrium blood pool	88.3
		Left ventricle blood pool	88.3
		Left ventricle myocardium	72.7
A4c	182	Left atrium blood pool	89.8
		Left ventricle blood pool	88.9
		Left ventricle myocardium	73.7
		Right atrium blood pool	88.1
		Right ventricle blood pool	83.3
PLAX	130	Left atrium blood pool	86.1
			87.9
			85.2
			86.4
		Anterior septum	76.8
		Posterior wall	74.9
PSAX	124	Left ventricle blood pool	79.6
		Left ventricle myocardium	74.0
		Right ventricle blood pool	64.6

Overall accuracy for individual images = 84%

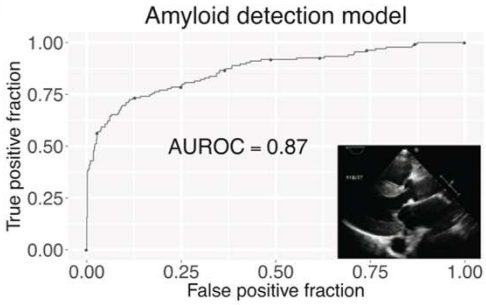
Zhang J et al, Circ. 2018; 138: 1623-35



Zhang J et al, Circulation 2018; 138: 1623-35
D'hooge J & Fraser AG, Circulation 2018; 138: 1636-8



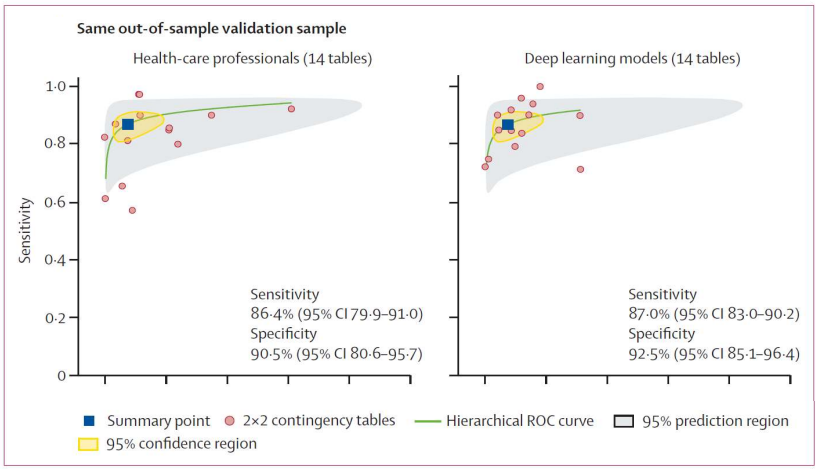
"An automated computer vision pipeline accurately assesses cardiac function"

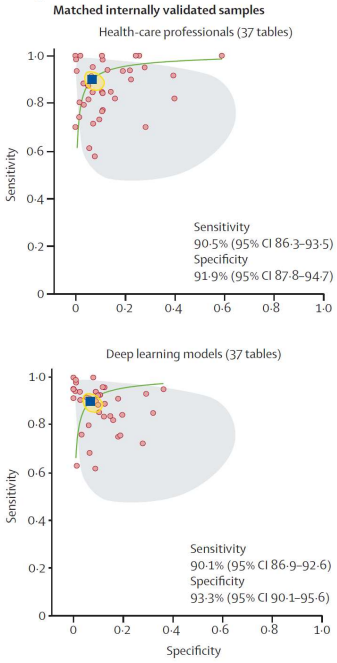


"CNNs enable detection of abnormal myocardial diseases"

Meta-analysis of deep learning for diagnostic imaging

25 studies with external validation, 14 in the same sample





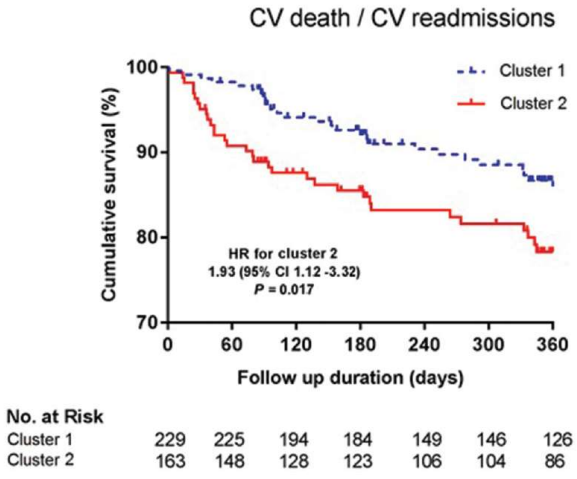
Liu X et al, Lancet Digital Health 2019; 1: e271–97

Media — Metabolic pathways to diastolic heart failure

SEVENTH FRAMEWORK PROGRAMME

k-means cluster analysis

392 patients
415 proteomic biomarkers
↓
2 clusters
17 independent biomarkers
↓
1.9 × excess risk of death or hospitalisation

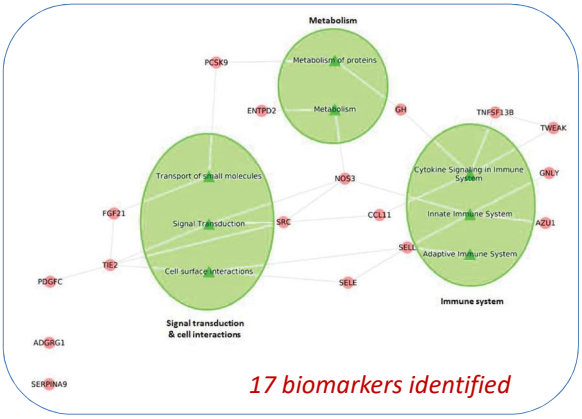


Stienen S et al, Biomarkers. 2020; 25: 201-11

MEDIA-DHF study (The Metabolic Road to Diastolic Heart Failure)

Enhanced clinical phenotyping by mechanistic bioprofiling

Unsupervised k means cluster analysis

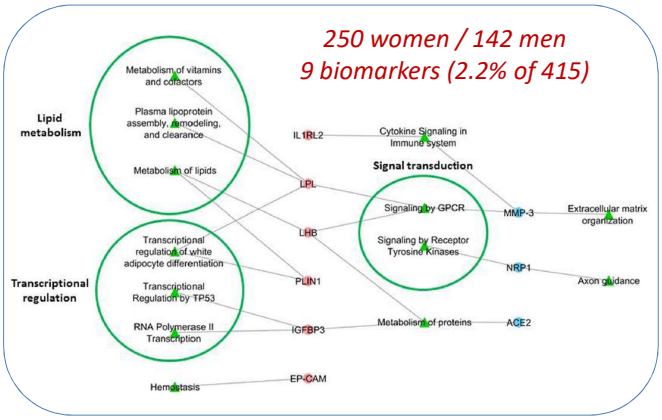


17 biomarkers identified

Stienen S et al, Biomarkers. 2020; 25: 201-11

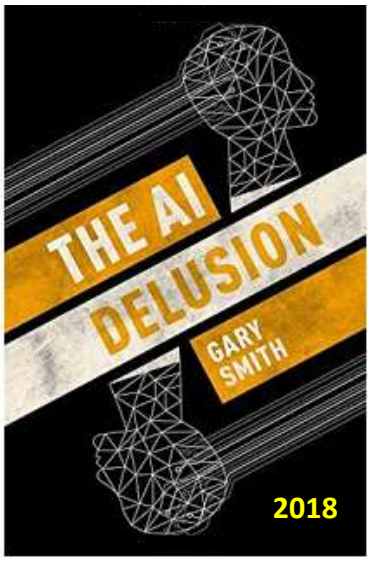
Sex differences in circulating proteins

Logistic regression analyses

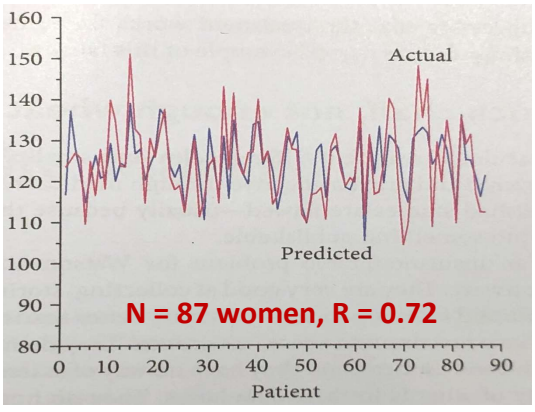


Stienen S et al, Biol Sex Differ. 2020; 11: 47

We underestimate chance correlations in big datasets



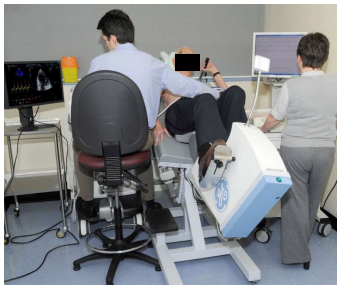
Prediction of systolic blood pressure

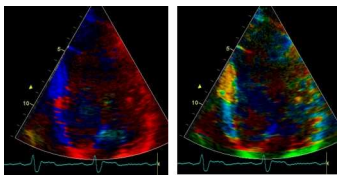


BP mean 125 standard deviation 10 mmHg
20 “characteristics”, randomly 0 or 1
20 normally distributed variables: 100, sd 10

Metabolic pathways to diastolic heart failure

Quantitative stress echocardiography
for LV longitudinal function, N = 156





>17,874 data points per subject

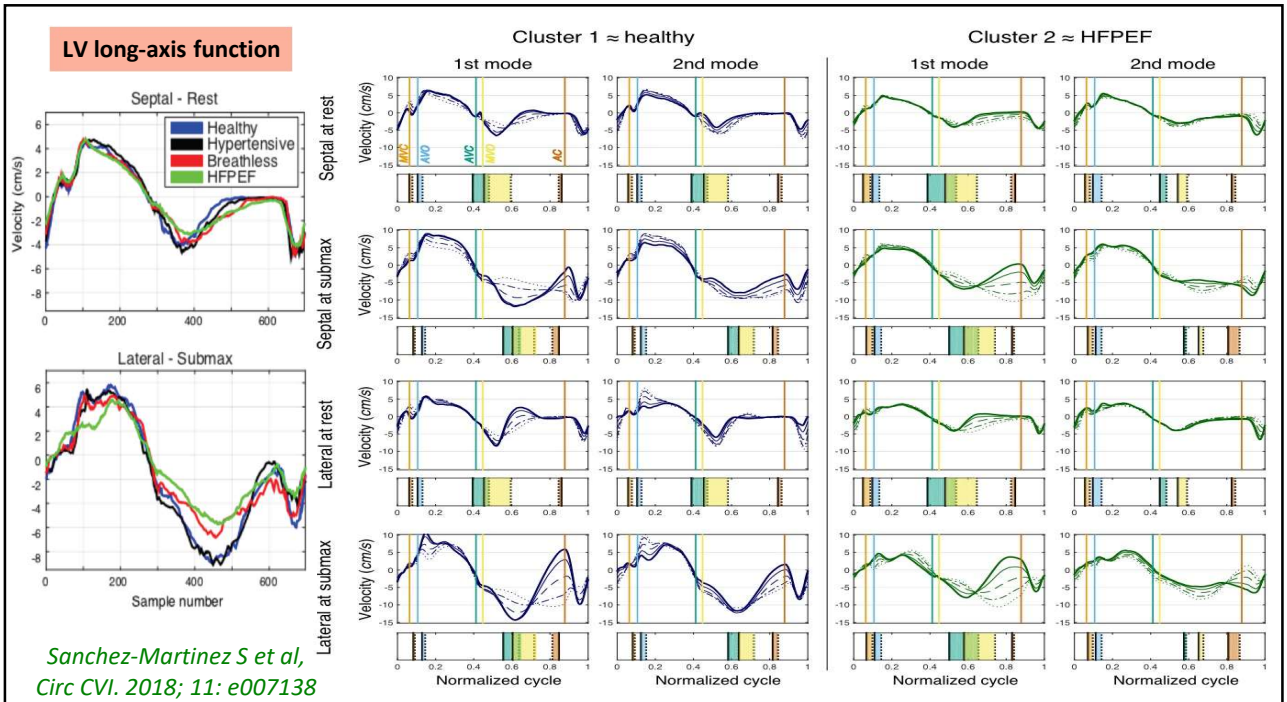
Velocity, strain, strain rate
in all 18 LV segments
↓
Imputation & alignment
↓
Principal component analysis
↓
K nearest neighbour

Velocity
in 2 basal LV segments
↓
Time alignment
↓
Multiple kernel learning
↓
Hierarchical clustering

Interpretation, visualisation of learned patterns

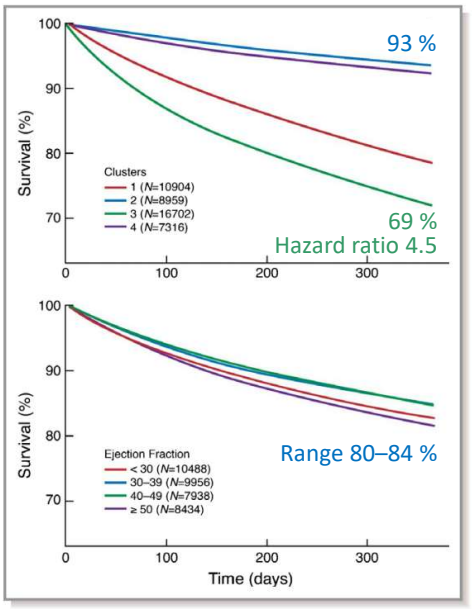
Sanchez-Martinez S et al, Med Image Anal. 2017; 35: 70-82
Sanchez-Martinez S et al, Circ Cardiovasc Imaging. 2018; 11: e007138
Tabassian M et al, J Am Soc Echocardiogr. 2018; 31: 1272-84

LV long-axis function

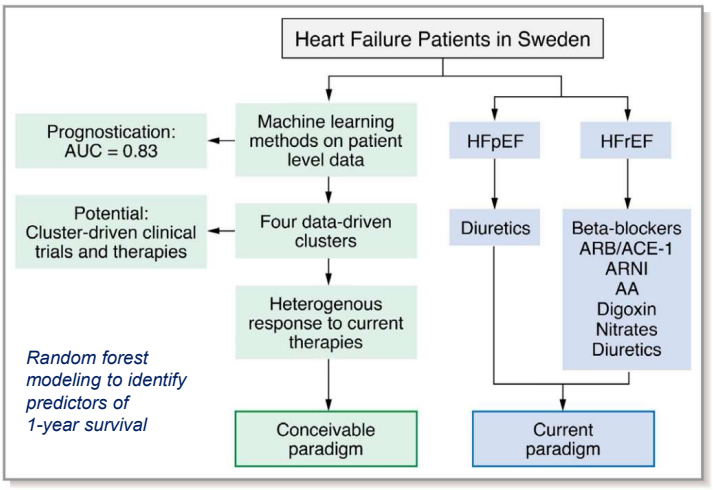


Sanchez-Martinez S et al,
Circ CVI. 2018; 11: e007138

Machine learning improves prognostication at 1 year in patients with heart failure



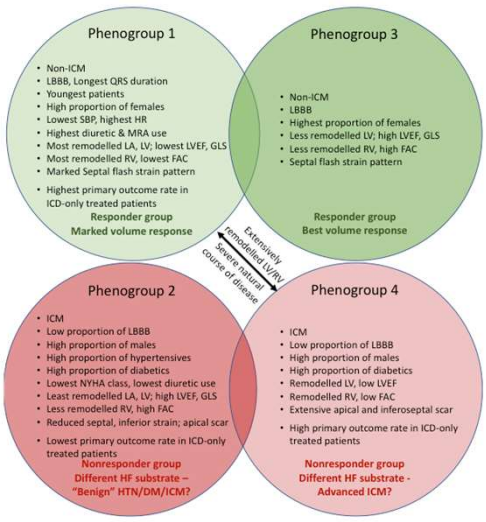
44,886 patients in the Swedish Heart Failure Registry

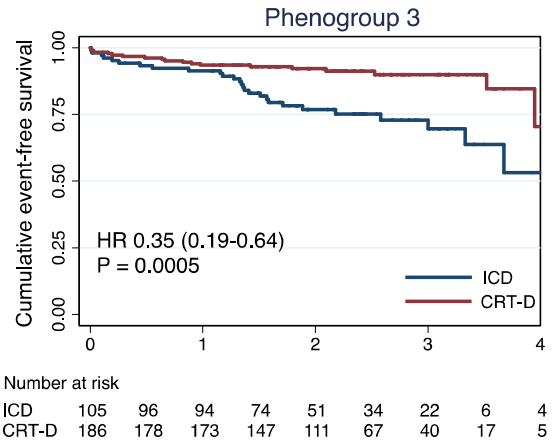


Ahmad T et al, J Am Heart Assoc. 2018; 7(8): e008081

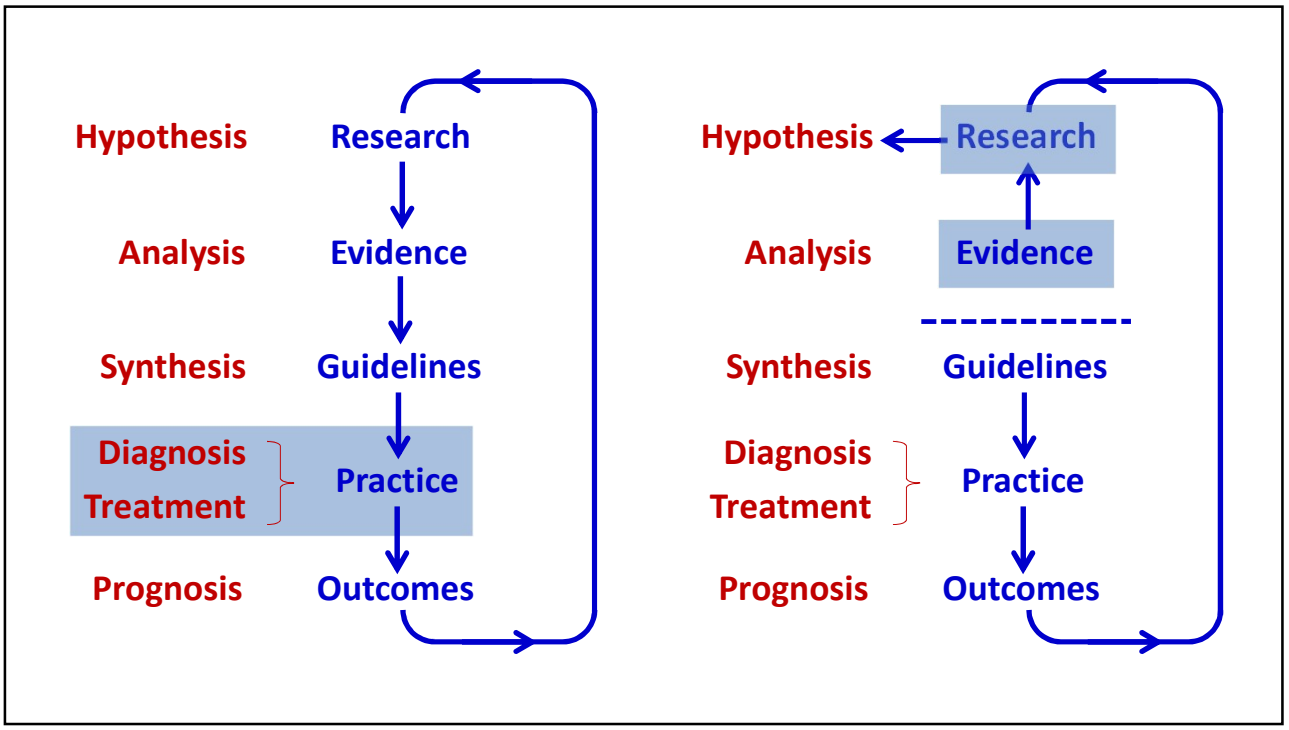
Machine learning to identify phenotypes of heart failure & response to treatment

1106 patients (LVEF ≤ 30%, QRS ≥ 130 ms, NYHA class ≤II) in MADIT-CRT





Cikes M et al, Eur J Heart Fail. 2019; 21: 74-85



Evaluation needs and challenges for machine learning

- We need standards so that safety and efficacy are encouraged / assured
- Professional reporting standards:
  - **SPIRIT-AI** Extension for trial protocols [BMJ. 2020; 370: m3210]
  - **CONSORT-AI** Extension for reporting [Lancet Digital Health 2020 Sept 9]
  - open access to code / analysis of performance errors
  - **PROBAST** to assess risk of bias [Ann Intern Med. 2019; 170: 51]
- Regulatory guidance
  - Definition of Software as a Medical Device [IMDRF, European Commission]
  - White paper on artificial intelligence and machine learning [FDA 2019]

CORE–MD
Coordinating Research and Evidence for Medical Devices

Developing guidance for the evaluation of artificial intelligence and standalone software in medical devices ***www.core-md.eu***

'MDR/IVDR – Artificial Intelligence regulatory challenges and opportunities'

Objective 1: Identify opportunities within our regulatory framework for AI, as well as the challenges we may face in addressing the topic:

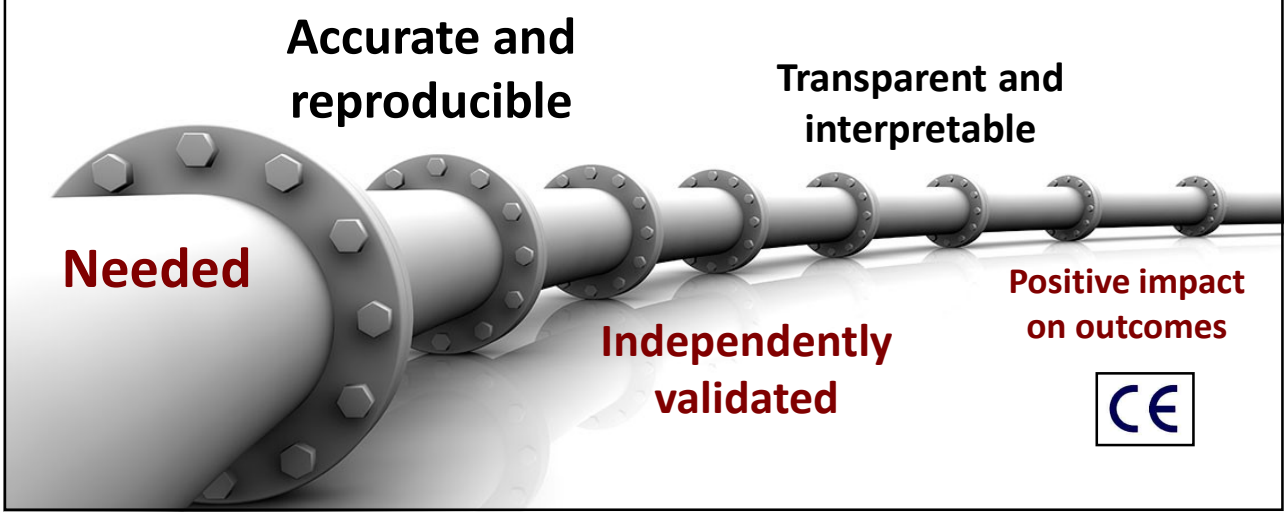
ESC European Society of Cardiology

- Risk assessment algorithm
- Relevant mitigation strategies
- Criteria to evaluate clinical performance
- Statistical standards
- Guidance on reporting of ML models
- Guidance on clinical follow-up
- Transparent post-market surveillance

	Clinical Application	Possible Risk
1	Research: disease understanding and modeling	Low
2	Diagnosis	Moderate or high
3	Prognosis	Moderate or high
4	Selection of therapy	High
5	Monitoring of patients	Moderate or high

Evidence submitted to Working Group on New Technologies
Caiani E, Hyafil F, Fraser AG, for ESC / November 2019

***Augmented intelligence* will be implemented in clinical practice when it is trustworthy, feasible, and ..**



UNIVERSITY OF CAMBRIDGE

Overview of Study Designs for Clinical/Other Studies for the Evaluation of the Artificial Pancreas

Roman Hovorka PhD FMedSci
University of Cambridge, UK

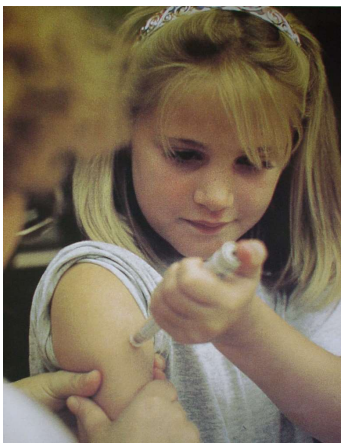
Duality of interest declaration

- Research Support: Minimed Medtronic, Abbott Diabetes Care, Dexcom
- Speaker's Bureau: Novo Nordisk, Eli Lilly, Dexcom
- License fees: BBraun, Medtronic
- Directorship: CamDiab
- Other: Patents

Content

- Type 1 diabetes
- What is closed loop (artificial pancreas)
- Commercial closed loop systems
- Pivotal study designs

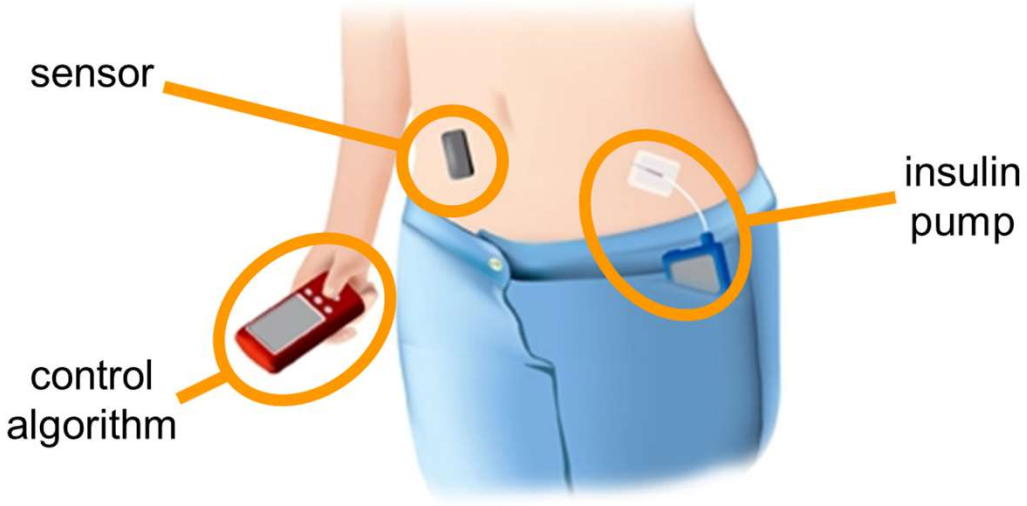
Type 1 diabetes



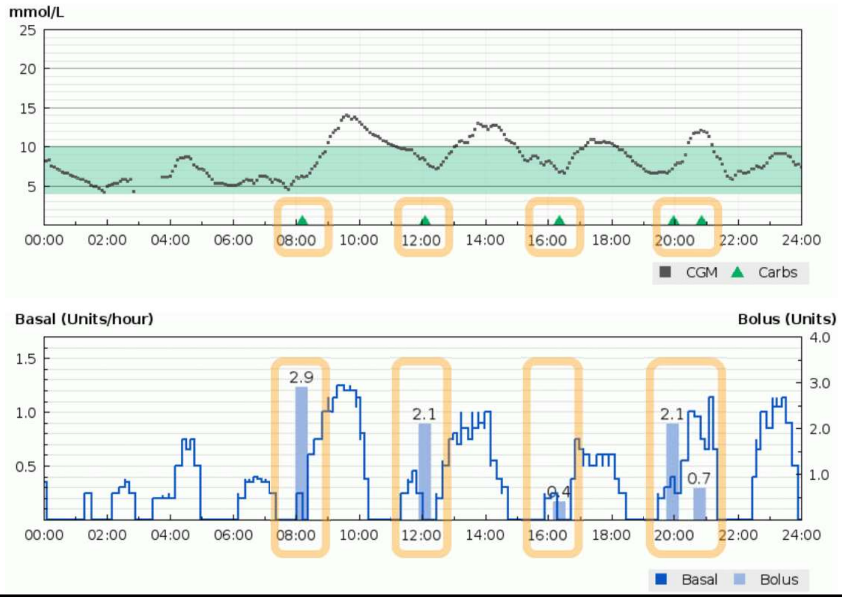
- Autoimmune disease
- No insulin secretion
- Lifelong treatment
- Goals of insulin treatment not achievable with present treatment strategies
  - Reason: day-to-day and hour-to-hour changing insulin needs

USA market
- $320B diabetes healthcare expenditure (2015)
- 1.3 million people living with type 1 diabetes

Artificial pancreas - automated insulin delivery

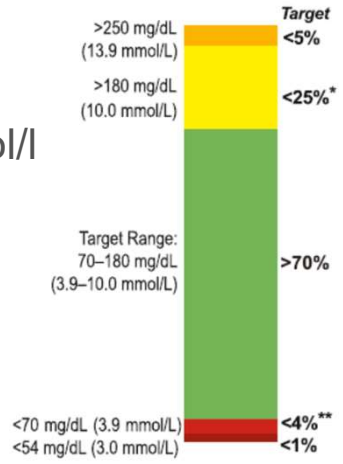


Hybrid closed-loop



What makes "good" artificial pancreas

- Safety
  - No increase in safety signals
- Efficacy – sensor glucose outcomes
  - Time in range between 3.9 to 10 mmol/l
    - Upwards from 70%
  - Low hypo exposure
    - Less than 4% below 3.9 mmol/l
- Low burden
  - Low alarm burden
  - Minimum technical issues



Battelino et al Diabetes Care 2019;42:1593-1603

Closed loop approved and in development

CE marked

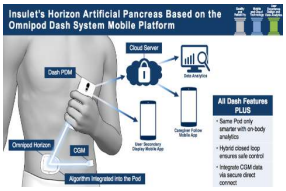
Medtronic

Tandem

Diabeloop

CamDiab

In pivotal studies/development



Insulet

Tidepool

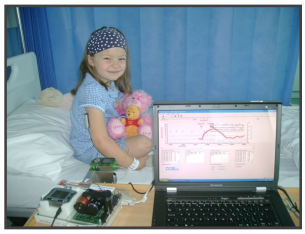
Beta Bionics

Eli Lilly **Roche** **Ypsomed**

Cambridge closed loop systems

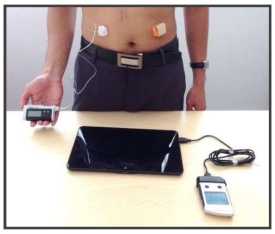
2007

2010

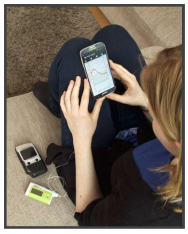


2012

2013

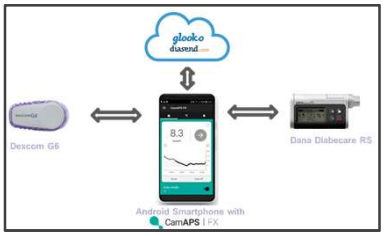


2014



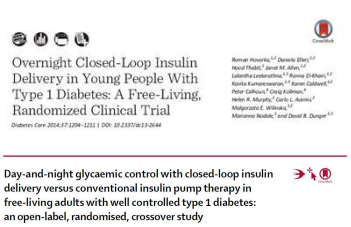
2016

2019

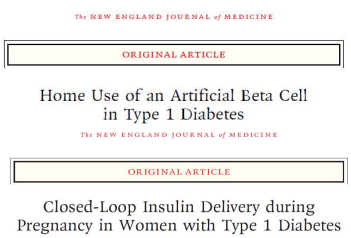


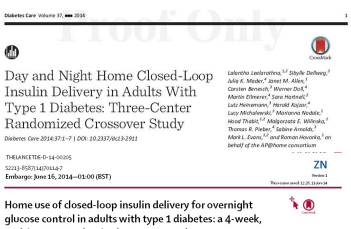
Clinical results

- Comprehensive outcome RCT data
  - Over 15 years of translational research experience
  - Young children, children, adolescents, adults, pregnancy
  - Reduced glycated haemoglobin, increased time in range, reduced hypoglycaemia, improved quality of life
  - All studies adopted RCT design


Overnight Closed-Loop Insulin Delivery in Young People With Type 1 Diabetes: A Free-Living, Randomized Clinical Trial

Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Home Use of an Artificial Beta Cell in Type 1 Diabetes
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes


Proof Only
Day and Night Home Closed-Loop Insulin Delivery in Adults With Type 1 Diabetes: Three-Center Randomized Crossover Study
Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study

Closed-loop in very young children – QoL

- 85% spent **less time managing** their child's diabetes with closed-loop.
- 90% were **less worried** about their child's glucose control when using closed-loop.
- 90% had **less trouble sleeping** whilst their child was using the system.

"Having the system working at school also for us was **reassuring**"

"My son was a lot more confident, less angry and **generally happier**"

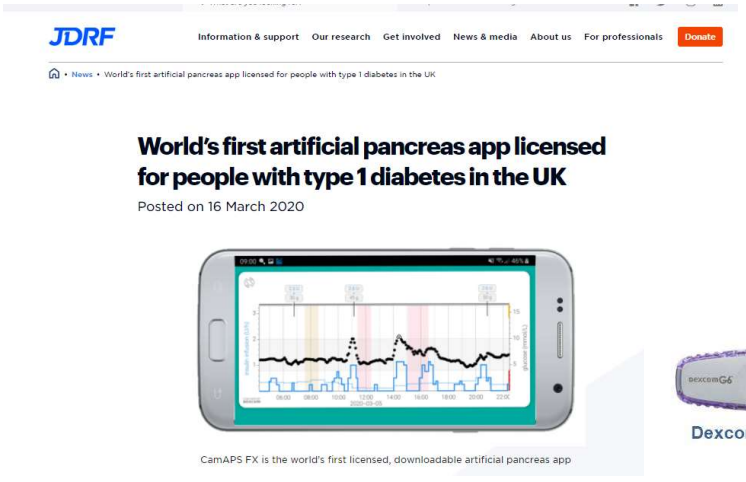
"first time we as parents were able to **sleep the night straight** since diagnosis"

"Also…our child…was able to **sleep undisturbed**"

"Overall we noticed the effect on our child's life: he had a significant **improvement in developing** his walking & talking,"

kidsap

Musolino et al. Pediatr Diabetes. 2019 Sep;20(6):794-799



UK Launch March 2020

Interoperable CamAPS FX app

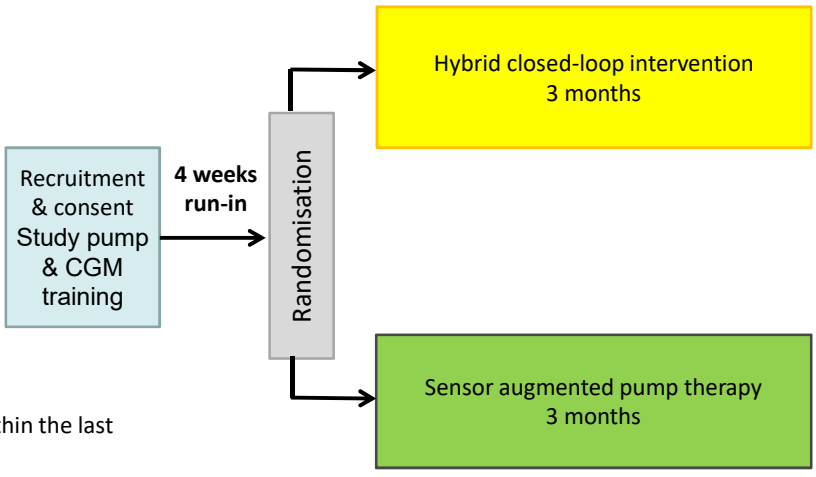
- Houses the hybrid Cambridge model predictive control algorithm
- Acts as “CGM receiver” alerts/alarms
- Incorporates a bolus calculator
- Automatic uploads data to Diasend
- Commercialised by CamDiab Ltd

CamAPS FX pivotal study design

- **Sample size: 84 participants randomised**
- **Primary endpoint: Time in target (3.9 to 10.0mmol/l)**

Inclusion
- Age ≥6 years
- T1D ≥ 1 year
- Pump therapy ≥ 3 months
- HbA1c ≥ 7.5% (53 mmol/mol) and ≤10 % (86mmol/mol)

Exclusion
- TDD > 2.0 IU/kg/day and <15 IU/day
- Pregnancy
- Hypo-unawareness
- Episode of severe hypoglycaemia within the last 6 months



CamAPS FX app results

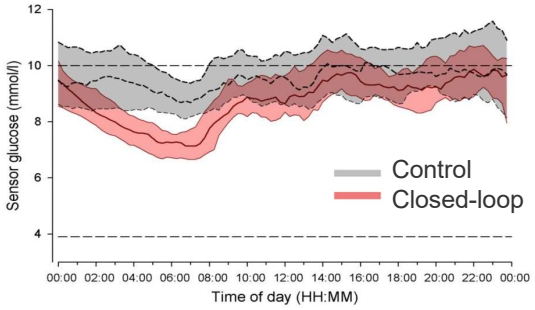
12 week RCT

- Closed loop vs SAP
- 6 years to adulthood (n=86)
- Six-sites
- Baseline A1C 8.3%

24 hour data

- Time in target ↑11%
- Mean glucose ↓0.8mmol/l
- <3.9mmol/l ↓0.8%
- HbA1c ↓0.4%

Improved time in target and time below target



Tauschmann et al Lancet 2018 392(10155):1321-1329

Medtronic 670G pivotal study: Single arm 3 month follow up

14 years and older (n = 123)

	Manual Mode	Auto Mode
Time in Range (71-180 mg/dL/3.9-10 mmol/l)	67%	72%
Time in Auto Mode (%)*	N/A	87%
Time < 2.8 mmol/l	1.0%	0.6%
Time < 3.9 mmol/l	5.9%	3.3%
Time > 10 mmol/l	27%	25%
Time > 16.7 mmol/l	2.3%	1.7%
Mean SG ± SD mmol/l	8.3±1.3	8.4±0.8

7 – 13 years (n=105)

Manual Mode	Auto Mode
63%	71%
N/A	81%
0.8%	0.5%
4.7%	3.0%
39%	32%
4.7%	3.7%
9.4±1.2	9.0±0.7

Bergenstal RM, et al. *JAMA*. 2016;316(13):1407-1408
Garg SK, et al. *Diabetes Technol Ther*. 2017;19(3):155-163
Forlenza G et a . *Diabetes Technol Ther*. 2019;21:11-19

Tandem Control-IQ

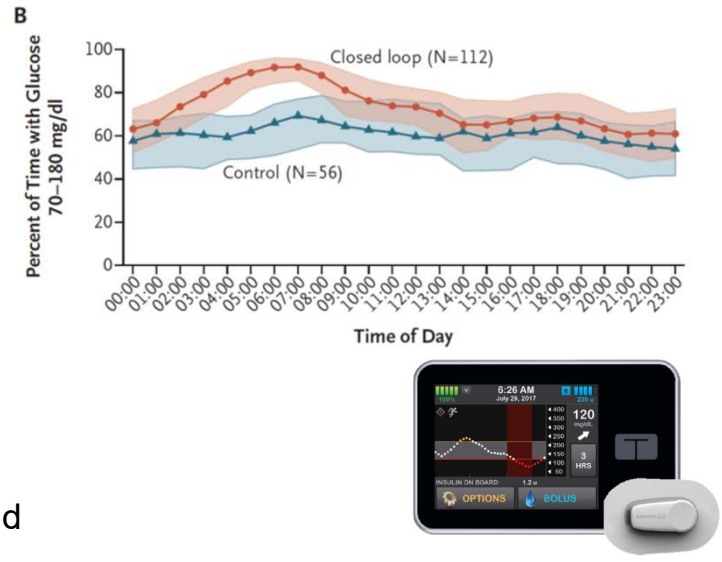
6 month RCT

- Parallel RCT
- Closed loop vs SAP
- 14 years to adulthood (n=168)
- 2:1 randomisation
- Eight-sites
- Baseline A1C 7.6%

24 hour data

- Time in target ↑11% (71%)
- Mean glucose ↓0.7mmol/l
- <3.9mmol/l ↓0.9% (1.6%)
- HbA1c ↓0.3%

Improved time in target and time below target



Brown et al NEJM 2019 Oct 31;381(18):1707-1717

Overview or pivotal studies

- Medtronic 670G
  - Single arm 3 month safety study
- Tandem Control IQ
  - RCT 6 month parallel safety and efficacy study
- CamAPS FX
  - RCT 3 month parallel safety and efficacy study
- Primary endpoint
  - SAE/severe hypoglycaemia (safety)
  - Time in target glucose range (efficacy)
- Populations
  - 14 year and older
  - 6/7 to 13 years
  - 1/2 to 6/7 years
  - Pregnancy

Drivers for study design

EU approval → used to be → FDA approval

FDA approval → is now → EU approval

Overview of Developments of Integration of Machine Learning into Diagnostic or Decision-support Software, Challenges for Clinical Evaluation from the Perspective of the Developer/ Manufacturer

Prof. Eigil Samset, PhD
Chief Technology Scientist
Cardiology Solutions
GE Healthcare

Your Partner in Heart Care

JB00846XX

presentation not approved for publication

3rd Workshop of the EUnetHTA Task Force on HTA and Medical devices Nov 4th, 2020

Moderated Discussion and Questions from the Audience

Chair – Tom Melvin

Minutes

- Morning session: 9.15-11.20
- Lunch break: 11.20-12.20
- Afternoon session: 12.20-16.15

Session 1 **Update:** ***Status Quo of the Implementation of MDR/IVDR and of European HTA***
Presentations about the status quo of the MDR/IVDR regulation and its implementation, as well as on the future legal design of European HTA and its progress in legislation.
Talk 1 by **Anna-Eva Ampelas,** DG SANTE updated the audience on the status quo of the implementation of the MDR/ IVDR: which structures, processes, methods (guidance documents) are already in place, and which are especially relevant for evidence generation (e.g. early scientific advice or post-market surveillance - two possible areas for collaboration).
Talk 2 by **Flora Giorgio,** DG SANTE updated the audience how the concept by the EC on European HTA and MD assessments – as presented in the EC proposal from Jan 31st, 2018 - was modified by the co-legislators and on timelines of further legislation and implementation processes. The upcoming legislation will provide a legal basis for a continuing exchange and collaboration between regulation and HTA also for medical devices.
1, Q: What is the estimated timeline for the EUDAMED database implementation? Will the use of EUDAMED be open for all? A: May 2022 is the target date. The original date was May 2020. It is extremely complex; we are talking about 6 different databases that need to be developed and work together. The aim is first to have a minimum viable product. From December 2020 a progressive roll-out of the different modules will be started. This will help all the actors to get used to the new system. A huge part of EUDAMED will be publicly available, a smaller part will be restricted (and that will be mainly for communication between the national competent authorities etc.). The database will be free of charge, but registration will be necessary for the different functionalities/parts. **2, Q: Besides the differences between medical devices and drugs there are also many common methodological principles in evaluating these technologies. What is done by the commission to support synergies between EMA, the MDCG and the new HTA regulation?** A: We are in the beginning of putting in place legal frameworks for both legislations. MD legislation is very new, complex and ambitious. It provides lots of opportunities for receiving more information and having a more structured information flow (between the

MDCG, EUDAMED, NBs, manufacturers, and the EC). We have to shift the mindset a bit to look at the products (devices) from a life cycle approach. The system will ensure that we put only safe devices on the market. HTA can play a role in ensuring and improving the relative effectiveness and the performance. There is a lot to be explored here. A lot of groundwork has been already done, a lot of experience is there to draw from (national, regional, EUnetHTA). What we need now is as bit more structure to fully explore the benefits.

3, Q: Now MDR /IVDR and the future regulation on European HTA is established under the same directorate general. The impact assessment for the HTA regulation indicated that 20 EU countries perform HTA of medical devices. How does the Commission (DG SANTE) ensure that the new MDR process takes this into account to ensure seamless medical device market access path? What is actually done by DG SANTE to support synergies?

A: The most concrete thing DG Sante is doing now is the creation of a legal basis for a cooperation between the 2 governing bodies (union bodies as it is called in the proposal) to enable synergies to develop. Creating this legal basis, the framework which is permanent for the HTA network, would facilitate this development. The synergy can develop pre-market in the form of early dialogue between the manufacturers and regulators, HTA bodies, which is important for the sector. But in terms of joint assessments, keeping the remit separate is very important. A joint assessment (according to Article 5) can happen only after the expert panel has given an opinion; this is a prerequisite to even fall into the scope, this will always be post-market approval. There is no mix of remit, no delay in market access. It was a big concern of the industry that the market access path would be changed.

4, Q: Regarding the structure and governance, there are a lot of subgroups, and besides the great opportunity, there is a risk of creating a lot of mini silos working specifically for what their remit and focus is. Having this in mind and reflecting on the experience of 20 years in the pharma sector, when the framework is approved and the implementation can start, the Commission should create the opportunities for exchange on the lessons learned on the process, and how to build trust (e.g. working groups, meetings, workshops, just like today's).

A: Yes, this is exactly the type of exercise we need. Getting the relevant bodies to talk with each other is what ensures breaking up the silos. The Commission's role is to provide the opportunity to do this. The workshop is exactly the kind of thing we need in the next years until the legislation comes into force because until we have a system up and running, we can create mutual understanding.

Talk 3 by **Tom Melvin**, Co-chair of the CIE
Presentation of templates and guidance documents (e. g. MEDDEV revision) of the CIE.

1, Q: Could you also provide information on how the process for the development of the templates and guidance documents works? What are the methods used, (e. g. were already existing templates for similar purposes reviewed), who has the possibility to comment on the drafts? How may the process allow for exchange with the HTA community? What's about public consultation as for EMA guidance documents?

A: The process how we decide what to work on: we send open calls to all the member states and ask what are the topics of interest, what they want us to address. We have standard templates to send around to partners where they can list what they want us to work on, what is the rationale, what they see as a deliverable. Then they prioritize on monthly meetings. After agreement, for each work item there is a term of reference, meaning agreement what needs to be delivered, what is the timeline, when will the consultations happen. In terms of how consultation feedback works, we consult on all the guidance documents. There are several consultation rounds (3-4, sometimes even more). The consultations are not full public consultations. We follow the terms of reference of the various working groups under the MDCG. We consult with observer members. So, we have the member states in the CIE working groups, and we have observer members. They are all part of the working groups. In general, they are all European organizations. So, we have lots of the clinical associations, Biomed Alliance, representatives of NBs on board etc. Through them, people have the opportunity to comment. Every single comment is analyzed and response is provided. In terms of the future and synergy, HTA colleagues could be brought to working group meetings (which would be a Commission decision to bring people into the working group level) and they could observe or take active role. In terms of the possibility for having public consultations, that would probably require the MDCG or the Commission to look at the terms of reference, because essentially, we are bound by that.

2, Q: In light of synergies expected between regulatory bodies and HTA bodies, has a meaningful presence of HTA experts been ensured in the expert panels responsible for the evaluation of the clinical development of MDs?

A: I cannot speak completely to the expert panels in this respect, this has been arranged by the Commission (sending the call out last year, getting the applicants and walking them through the process). From the member state perspective, we would have supported MDCG subgroups. In terms of HTA presence, I do not know, there has been a free call. I do not know the full list of experts, there are over 300, so I presume there are some with HTA background.

3, Q: Besides of the Summary of Safety and Clinical Performance, which will be made publicly available in EUDAMED, may the content of any of the templates of the Clinical Evaluation Report and the Clinical Evaluation Assessment Report be made available to European HTA or national HTA agencies?

A: This will be a policy and a legal consideration. Historically, clinical evaluation report would typically be considered by the manufacturer to be commercially confidential. HTA and regulators think that either the manufacturers' clinical evaluation report or the NBs' clinical evaluation assessment reports should be made freely available. Under the MDR rules, there is not a specific rule relating to either of these documents. MDR is somewhat

silent about it, but generally these documents are considered commercially confidential. This is possibly something for the Commission to decide, in terms of the policy side and the legislative aspects to it. We did a lot of work on the standardization on what clinical evaluation assessment reports would look like and this is already a big step. This is around the technical part. Around the legal part and access to it, this is something the Commission would need to take further. A DG Sante: with the HTA proposal the framework and legal basis is set up to enable information sharing (in the appropriate time with appropriate confidentiality measures). After the proposal is adopted, in the implementation phase, an implementing act/ guidance document will be needed to give details on structure (at which phases and which type of information exchange could take place).
Talk 4 by **Françoise Schlemmer**, Team Notified Bodies Analysis of challenges and experiences with the implementation of the new regulation; gap analysis and needs assessment for support of Notified Bodies. Change of Clinical Assessment by Notified Bodies in the Light of New Regulations.
Q: In the MDR NB have to have much more clinical expertise then under the MDDirectives. Which role do you think will evidence based clinical guidelines and evidence-based medicine play in the clinical expertise established in NB? A: NB have hired a number of clinical experts to join their teams in order to be able to assess the manufacturer procedures, documentation and data that are provided. Guidances allow further and better harmonisation of the practices among the different NBs and members.
Session 2 Appropriate Evidence for Regulation and HTA for Software Classified as High Risk Medical Devices
Talk 1 by **Nada Alkhayat**, Chair MDCG Working Group New Technologies presented an introduction to classification of software as (high-risk) medical device and the guidance on the MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/ Performance Evaluation (IVDR) of Medical Device Software.
No questions
Talk 2 by Dr. Abtin Rad, Global Director Functional Safety, Software and Digitization, TÜV SÜDs talked about experiences with software evaluation under the MDDs and challenges under the MDR.
1, Q: A lot of attention needs to be paid to all the different aspects, definitions and new things are coming in that you highlighted, specifically about cyber security, and privacy

aspects. There is a lack of standards across the EU and a lot of things refer to the state of the art, it is interesting to figure out where you are getting the definition and the elements of the state of the art and how they are defined, what is the scope for that?

A: Very good questions. This is a question that we often need to discuss with the manufacturer, as well as with the regulators. What we do to identify state of the art is that usually we look into harmonised standards, if there are new versions of that standard, look into current state of standard. If there are no standards, we perform a literature review. When we look at a very new emerging field, which is AI topics, there are no standards, no regulations, almost nothing available, except for very few countries e.g. only Chinese have regulation in place already. Even on standards we have not much, we have the P7000 standards from the IEEE, however, for the medical field there is not much. So, what we do then is to look into literature analysis, what is the common approach, what is the best practice currently, for instance how much data do we use for the training and for the verification of the model. There are no numbers, but the literature analysis that we have done, we found out that it is approximately between 70-80 and 20-30 resp. This is how we approach state of the art.

2, Q: Do you have any specific framework to help companies to give you the required documentation you mention for MDs with AI?

A: The problem with the NBs is that we cannot say what should be delivered and consult in this case. That is something that the regulators have to do, it is their authority to do that. However, we have published (together with all the NBs in Germany) a document, which specifies what we expect from the manufacturers for AI. It is a list of around 150 questions and documents necessary for the assessment. This is what the interest group of NBs in Germany does, they can provide this list, it is publicly available. This is only an interest group opinion and not binding.

3, Q: Do you have a framework for this? And how do you determine the evidence/and evidence level to be submitted? To what extent is this harmonised to SaMD frameworks and e.g. the AMIA regulatory framework (FDA)?

A: Is it specific to one question, is it specific to a question on SaMD in general? This is not a decision we can make anyway. We only look at what the regulators give us as homework and we implement it. AMIA documents and standards are applicable for FDA only and not applicable for us. We only rely on what the EU commission gives us on regulation and guidance documents. That is our approach. When it comes to harmonisation on international level, this is something the IMDRF is working on. The European Commission has done a great job regarding the classification rule, they explicitly refer to IMDRF risk classification matrix, which is kind of international harmonisation.

Talk 3 by **Joanne Holden**, CHTE Associate Director - Medical Technologies Evaluation Programme and Interventional Procedures Programme, National Institute of Health and Care Excellence, UK

presented the framework for e-health and experiences from HTA bodies of the assessment of software classified as high-risk medical device.

1, Q: Is the independent assessment group a dedicated one for all digital health technologies (DHTs) or for each DHT?

A: We have a contract with about 5 external assessment centers all around the UK, so it is not the same for each DHT, it could be by any one of those that we commission the work from.

2, Q: At NICE, do you have any expectations how many digital health interventions per year will fall under Tier C (i.e. "high-risk" digital device)?

A: It is hard to say. What we can say is, that it is more likely that we will see the value of what we do in the NHS for tier C, but this might be proven to be wrong. At the moment, a lot of our capacities is used for tier C. We may have a better idea in a year's time and perhaps we are able to share it then.

3, Q: Do the NICE risk classes correspond to the medical device regulation risk classes?

A: Not entirely. On the NICE website there is an evidence standards framework page dedicated to DHT (https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies). There will be a document published next month about the overlap between the MDR and evidence standards framework.

4, Q : Have you been collaborating with the MHRA (Medicines and Healthcare products Regulatory Agency)?

A: We have had quite some collaboration with the MHRA in the evidence standards framework. Now the MHRA's attention has turned to the UK's conformity assessment process. We have a lot of collaboration, but not necessarily on the HTA, because that is not the MHRA's area of focus.

5, Q: How long does the assessment process usually take, from the submission to the final report, including all the consultation and stakeholder meetings?

A: The MD program is intended to be done in 40 weeks from selecting the topic through assessment and full public consultation to finally getting the publication out. In the digital tech health programme it is intended to be done in 17 weeks. This time, because of Covid-19, there has been some delay.

6, Q: Does your framework set expectations on evidence for the interaction of technologies with human users? You didn't mention this and presently there is a gap between in silico evidence of function and clinical trials of mature interventions where

this is a very important issue. Technologies will be used and trusted by humans in a range of ways and this has been largely overlooked in current research.

A: It is a good point. We have not been so prescriptive in that way and the reason is because our process involves a committee deliberation where it is probably the best to have individual discussion on that human element. In the technologies that went through the process, there has been a lot of public discussion about this. The Committee would discuss this element until they would feel happy with the information that is put in front of them.

Talk 4 by **Alan Fraser**, Chair, Regulatory Affairs Task Force of the Biomedical Alliance in Europe
presented examples of use of machine learning algorithms in cardiology and on the evaluation needs and challenges from the perspective of the clinician.

Q: Could you elaborate on the need for technical and clinical explainability and how this can be achieved?

A: Good question and one that we will be addressing with the CoreMD consortium (that is led from university in Leuven). It partly depends on the specific machine learning or AI method that is used for specific clinical applications. When it does not need to be interpretable, when it is just measuring an image as long as we know very well the diagnostic performance and the training set, generalisability and applicability of that tool, but for more advanced clinical decision support based on the analysis of larger datasets, I think we need algorithms that are interpretable. I know that engineers are looking at methods of trying to work out what goes on inside a neural network so that they can tell us. I am not an expert in that, but for the studies that we have done, and the dimensions we used learnings where it was possible to identify how the algorithm separated subsets into clusters. I personally would have more trust in such a tool for clinical purposes, it is a very valid question and I am sure we do not have detailed answers yet.

Talk 5 by **Roman Hovorka** , Prof of Metabolic Technology, University of Cambridge
provided an overview on study designs for clinical/other studies for the evaluation of the artificial pancreas, which contains a control algorithm to deliver insulin.

Q: Question from the patients' perspective. You said that FDA approval is now preferred because the bar is lower. Does this mean that in the EU the regulatory requirements have patient benefit higher or it would be too fast to make this conclusion?

A: In case of diabetes, new types of devices were introduced and allowed to be marketed with 510(k) instead of PMA (pre-market approval). It is easier for other manufacturers because they just need to show equivalence. Patients created their own system outside the regulatory environment, and the FDA thought that it is safer to make it easier for

manufacturers to get into that space and to move people from this system to regulated space. This process is not reflected on within the European approval process.

Talk 6 by **Eigil Samset**, Chief Technology Scientist, Cardiology GE Healthcare provided an overview which developments can be expected in the next years concerning the integration of machine learning into diagnostic or decision-support software and what are challenges for clinical evaluation from the perspective of the developer/ manufacturer.

Q: You touched upon the increased risk which is going up with the increased complexity, if we start using AI and machine learning. It will look at the level of applications. Automate interpretation and things that can be done in that level. Potentially it might be a mine field due to the challenging situation with correlation and causation. Machine learning that is about correlation more than anything and causation. Nature of machine learning needs to be well understood. Can you please give a reflection on the role of the physician.

A: We are not trying to replace the physician, we are trying to empower the physician, not really provide anything that replaces their current decision making, but giving them new tools in their toolbox that help them see potentially new association or help combine new information that might have otherwise been overlooked with the insight that they have. This goes back to the explainable AI and contextualisation, that we need to look at this not as black magic, not like black box solutions either. Strive for providing tools that can be explained and contextualised, so that the physician role as the ultimate responsible is maintained but we just want to make the physician perform even better but taking into account the amount of data that is almost impossible for a human being to process without this type of tool to aid them.

Panel session of all presenters of Session 2, Tom Melvin, Francoise Schlemmer and in addition Matthias Perleth from the Joint Federal Committee in Germany, another representative of a HTA body

1, Q: Evaluation of machine learning software is a hot topic of concern at the moment in clinical speciality associations (Comments of the ESC to EU White paper AI, letter of the American Association of Radiologists to the FDA), but what do you expect from your experience in your area (regulator, NB, HTA, clinician) which types of software or software applications in the high-risk classes will be the most frequent ones to assess? Which types are challenging and why?

Tom Melvin: from my own personal experience, there are products like decision support tools for someone who might have a stroke or CVA to help decide whether there is a bleed or not from an urgency T-scan to direct thrombolysis. This is literally a piece of information

that can be life or death for informing decision steps, so I guess there is radiology one that comes to my mind.

Alan Fraser: Difficult question. I think the highest risks would be relying on recommendations for decision support based on algorithms that we cannot fully understand and interpret, because we then may make mistakes and we may not even understand why to improve the system. I think it is interesting that professional recommendations for AI now suggest that every published manuscript should include an evaluation of errors of the algorithm and why those happened, which is very sensible, so that we can learn how to improve performance. On the other hand, we know from studies of clinical decision making that all of us are likely to be prone to at least one diagnostic error during our lifetimes and the prevalence of diagnostic error in some estimates is up to 30% or an average of about 15% in different reports. Yes, we need support but it should be intelligible and I like the idea that as a clinician you are juggling different probabilities of disease and outcomes and responses and if we can narrow the range of those probabilities with more insight into the data using machine learning, that will help us. But rather than saying that the type of AI or ML is high-risk, I think it is the application what is really important. I think also the greatest risk is when we have tools that haven´t been adequately validated, when they are not really generalizable or they have been developed in women but they are applied in men, or in adults but they are applied in children and so on. We need to be very sure that the tools that we use can be used safely and accurately in the population for which we use them.

Roman Hovorka: Coming from a slightly different angle - I work in the space where people need to dose insulin every day and they do make wrong or right decisions and I just want to add to this discussion that the risk needs to be judged against existing risk (that people make right or wrong decisions). I think it is important that we are not looking for absolute safety or absolute risk reduction, but we are looking for relative risk reduction compared to the current existing risk. That risk could be due to medical professions making incorrect decisions themselves as Alan was saying or the users in this case type 1 diabetes making their own mistakes as well. The only way to assess safety is through clinical trials. In clinical research often the systems are evaluated, but quite often the interaction with the users, (the user component) also impacts the performance, so it is quite a complex issue, which is difficult to assess.

Tom Melvin: Working as a regulator we became aware in recent years about the hack in algorithms in the old insulin pumps and the communities that existed to drive that and it is very interesting to see that hopefully the new products with ongoing clinical studies will provide a more sustainable and evidence-based approach to that.

Francoise Schlemmer: For high-risk products, as well as other kinds of products, when they are innovative, they should go through the panel expert review, to have a proposal of views from these experts and of course as it was said earlier there are probably few guidances, probably a few things are to be addressed for a better harmonization of NB. Team NB has set up a task force to take on board aspects regarding mobile applications, and probably there will be other aspects that will be taken into consideration in the future.

Eigil Samset: I touched upon it, we are moving away from tools that are automating tasks that are already being done to decision support and we all just need to realize the risks involved in that. The comment from Dr. Hovorka was very good. It needs to be done in a relationship to the risk that we currently have with either or not having such tools that are based on guidelines that may be good but typically have a very long lead time from the day of initial evidence is being generated to meta-analysis until they are being released in those guidances. If there are new associations, or better models that can improve outcomes, I think we need to welcome that, obviously we need to validate it against to current state of care.

2, Q: As many of the present (pharmacological) treatments are validated in clinical trials without us understanding the pathophysiologic intricacies of the effect, should we be so wary of black box AI?

Tom Melvin: It speaks to this kind of balance we spoke about earlier and I think Prof. Fraser described it really well. Worrying about the intricacies of the black box is less of a concern when there is robust published evidence to show possible patient outcomes or at least how the algorithm worked with the input to create the output. For me it makes sense, it is fair to worry less about workings of the algorithm how it works when there is the evidence there to support it from the assessment that´s been done.

Alan Fraser: The question is very fair, but we also need to reflect on the difference of the amount of published and available evidence usually for new drugs compared with new devices. New drugs will usually have very large pivotal trials. In cardiology maybe 10 000-15 000 patients. We rarely see device trials of that size. The evidence isn´t so secure. It is about the safety of the conclusions that we can draw. And secondly about the post market surveillance, because with drugs we are more used to looking for side effects and we really do not yet know how we are going to do the post market surveillance of AI. An issue that is covered in the legislation is, if it is a medical device and if it is high-risk, but I would be interested to know from Tom or anyone else in the panel if you think we have started to consider how we can address that seriously. If that is in place and if the trials are large enough, I think the question is fair and the comparison would be reasonable and it would be appropriate to use new tools based on AI even when we do not completely understand how they reach their conclusions if the associations with endpoints is secure.

Tom Melvin: In terms of my perspective as a regulator, I don´t have personal experience with an assessment of this, but we have looked at these types of products in specific scenarios (e.g. as a result of COVID we had derogations for the urgent need for products and some of it was to help triage and support clinical decision making in the context of COVID, some was e.g. helping to conduct trans-thoracic echo). In terms of perspective of clinical investigation and AI based software, it is a challenge of our current pathways, current procedures, current protocols, and all of that kind of thing, where historical datasets presumably are used to validate algorithms. From the regulatory perspective at the CIE working group, we don´t have any work items planned per se but it is something we would like to discuss with the new and emerging technology group.

Eigil Samset: Alan made a good point with regard to the amount of evidence in pharmaceutical trials compared to what you do in medical devices. Honestly, I don´t think

it is realistic that we can see that type of evidence for MDs. Pharmaceutical drugs might be on the market for decades without changes. MDs are typically updated, new versions come every year or maybe even more often. Margins of the pharmaceutical industry are incredibly bigger than for medical devices industry so having that type of cost associated with creating that amount of evidence for MDs, I think is unrealistic, on the short run at least.

Roman Hovorka: I would like to second this, this is a point that I wanted to make as well. There is a distinction between pharma development and MD development and speed of development, finances are also challenging. One way to move things forward is to think about innovative ways how to evaluate in post market surveillance, we need safety of these products as they develop and evolve.

3, Q: How frequent does the software in an artificial pancreas or an AI-guided imaging machine require a new version? What type of clinical data is required to obtain CE approval for such (apparently) minor modifications of software?

Tom Melvin: In case of amendment of products, if it would constitute a significant change, the manufacturer would need apply to a NB to have an assessment done before the change is integrated. In general, with software-based products, iteration or change is a much higher pressure than with medicinal products. In general, the software community has a constant desire for change. Many of these changes may not be significant. Other changes, e.g. to the algorithm, are considered significant because they may affect output data in line with intended purpose of the product. This can happen sometimes in the diagnostic setting, that a software developer changes the sensitivity or specificity of the algorithm, which can have an impact on the overall safety of the product. To me it is about making sure that the software experts responsible for the algorithms have good outreach to clinical experts who are supporting the clinical evaluation, and there is a clear pathway to make sure that anything that can affect safety or performance has a good procedure applied.

Francoise Schlemmer: In case of significant changes, there is a need of informing the NB and it needs to be reviewed by the NB.

Matthias Perleth: From the HTA perspective, a new assessment will become necessary in case the indication changes significantly, e.g. an additional patient group will become eligible (a different age group, different risk factor profile or different disease stage), or safety or effectiveness would change fundamentally with the iteration of software. A new assessment could be triggered also if qualification requirements change significantly. Sometimes we could think about transfer of data to a new field of application in case of a software. For example, if a diagnostic device detects a pathology that is common for different diseases (e.g. macular degeneration).

4, Q: Do "significant changes" need to show an increase of efficacy? Only implementing a significant change without additional effectiveness or efficacy produces now additional value.

Tom Melvin: An increase in efficacy is not a sole criterion for a significant change for a NB assessment. Significant change will be defined typically what falls under the manufacturers' quality management system, so if change is made to the product or the technical documentation, the manufacturer would have rules. It is not simply linked to the safety or efficacy of the product, but to what is the nature of the change that is being made and this would trigger the manufacturer to think about it if the change is significant or not.

Alan Fraser: if you look at the proposal on AI from the FDA, they have something which is called the algorithm change protocol. It means that the manufacturer should identify in advance, what aspects of the software may be prone to development and iterative change and agree with the regulator, whether those would need to go through clinical evaluation or could be approved on performance criteria. So, there may be ways to categorize iterative changes as minor and potentially major. At least for imaging diagnostics, a central database would need to be developed, which could be used by all the manufacturers for comparing the performance of their software.

Tom Melvin: That is the FDA white paper on artificial intelligence.

5, Q: How can we imagine by which means post-market follow-up evaluation would identify a relevant deterioration in the benefit-risk ratio in a software application and what would happen? Will such information be available to European HTA, national HTA bodies, clinicians, patients? To HTA bodies: How will HTA deal with it?

Tom Melvin: A huge amount of detail has been given to the methods and procedures the manufacturers should have from monitoring the product in the post market. We have post market clinical follow-up, periodic safety update reports, periodic safety reports, general post market surveillance system to capture any complaints or adverse incidences. How that works with the manufacturers of software-based products and how the overall benefit-risk might be challenged in the post market, is something that is an important consideration. We talked a lot in this session about change iteration, and it is really an important issue in software products. Sometimes a change can affect the algorithm which is related to the safety or performance of the product, which may lead to potentially negative benefit-risk ratio. In general, there should be a post market surveillance system with all types post market reports, backed up by a risk management file that would consider things like misunderstanding by a clinician etc. If that occurs at a certain level than that would hopefully trigger corrected and preventive actions by the manufacturers. In general, this is how I would see this system. In terms of how this information would be available to the HTA community, this is a little bit like the discussion earlier, there is presumably more policy and procedural work to do to in this matter. In general, with the MDR there are improved rules for making incident reports and findings through the new EUDAMED system available, but this is going to take some time.

Francois Schlemmer: It is clear that on one hand we have to respect the confidentiality, but once the deterioration is clarified we probably should consider putting it into EUDAMED, then it will be publicly available. The NB would need to inform competent authorities about such kind of information as far as EUDAMED is not concerned yet and

when EUDAMED will work competent authorities should receive information through specific email information from EUDAMED.

Eigil Samset: It was mentioned by NB before, that the state of the art is moving very fast and NB and regulators might want things to move slower, while innovators, companies, researchers would like things to move very fast. When we talk about post market surveillance, this might be an alignment of incentives, because in order to improve products that are based on data, innovators, manufacturers, researchers, would like to get even more data from post market surveillance to understand when a decision of a software is being overturned by a user if there is a degradation or typically more data will improve the product. I think what we will see is more in-built real-time performance model monitoring of products in the field, this is going to be easier in the post market surveillance. All this data can be used to improve products. Maybe engineers in the past have forgotten about post market monitoring, left that to the regulatory affairs, moved on to the next version. Now we will see a need for building that into the products, exploiting that data for improvements.

Roman Hovorka: I couldn´t agree more. The challenge is about the GDPR and privacy data. Need to collect data for improvement of the product, which in principle could be justified because of the post market surveillance. So, we might have some challenges between the need to collect data for performance improvement versus privacy issues.