Notified body view on evidence generation software

European Society of Cardiology Roundtable Meeting, Zurich.

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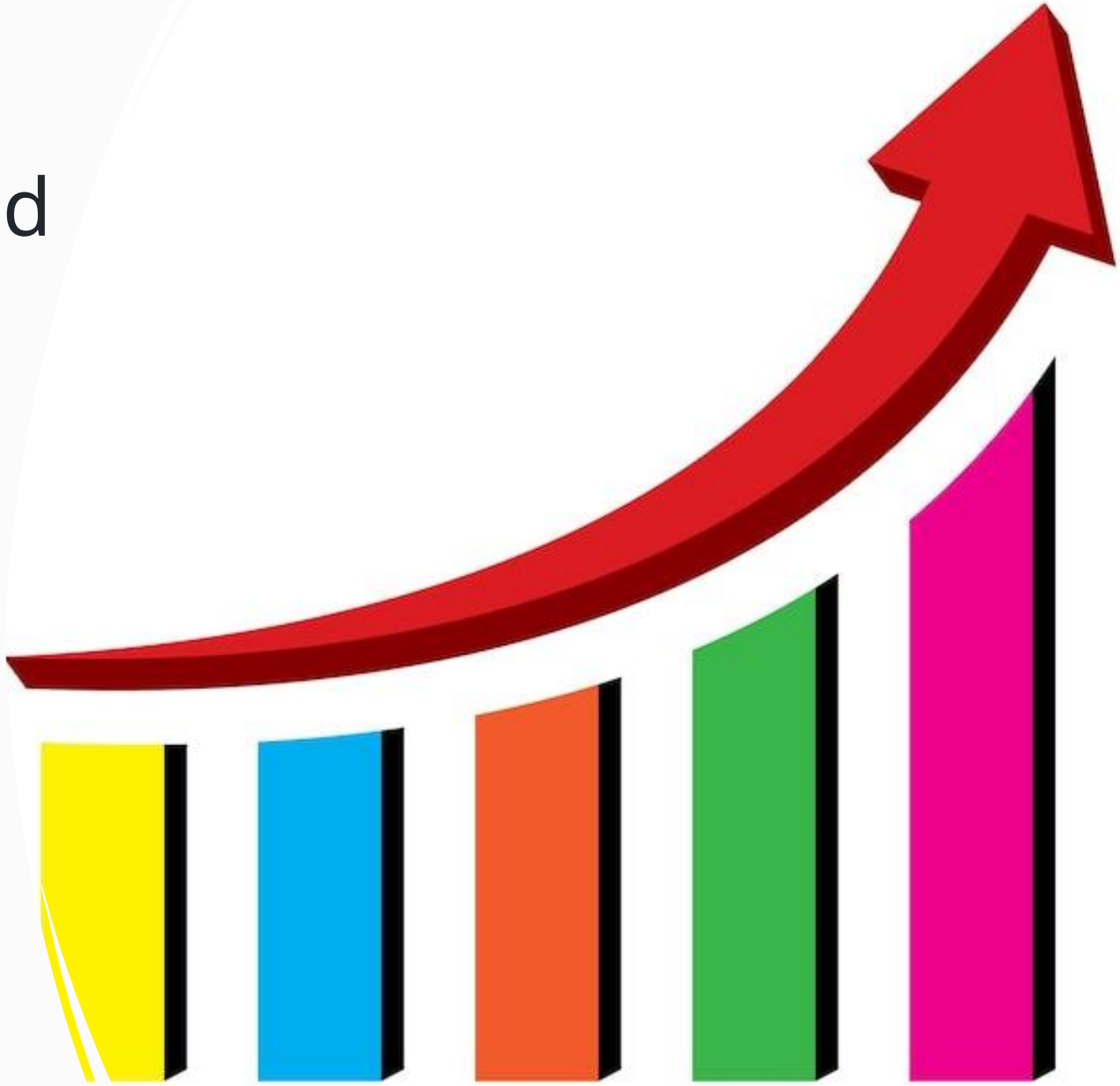
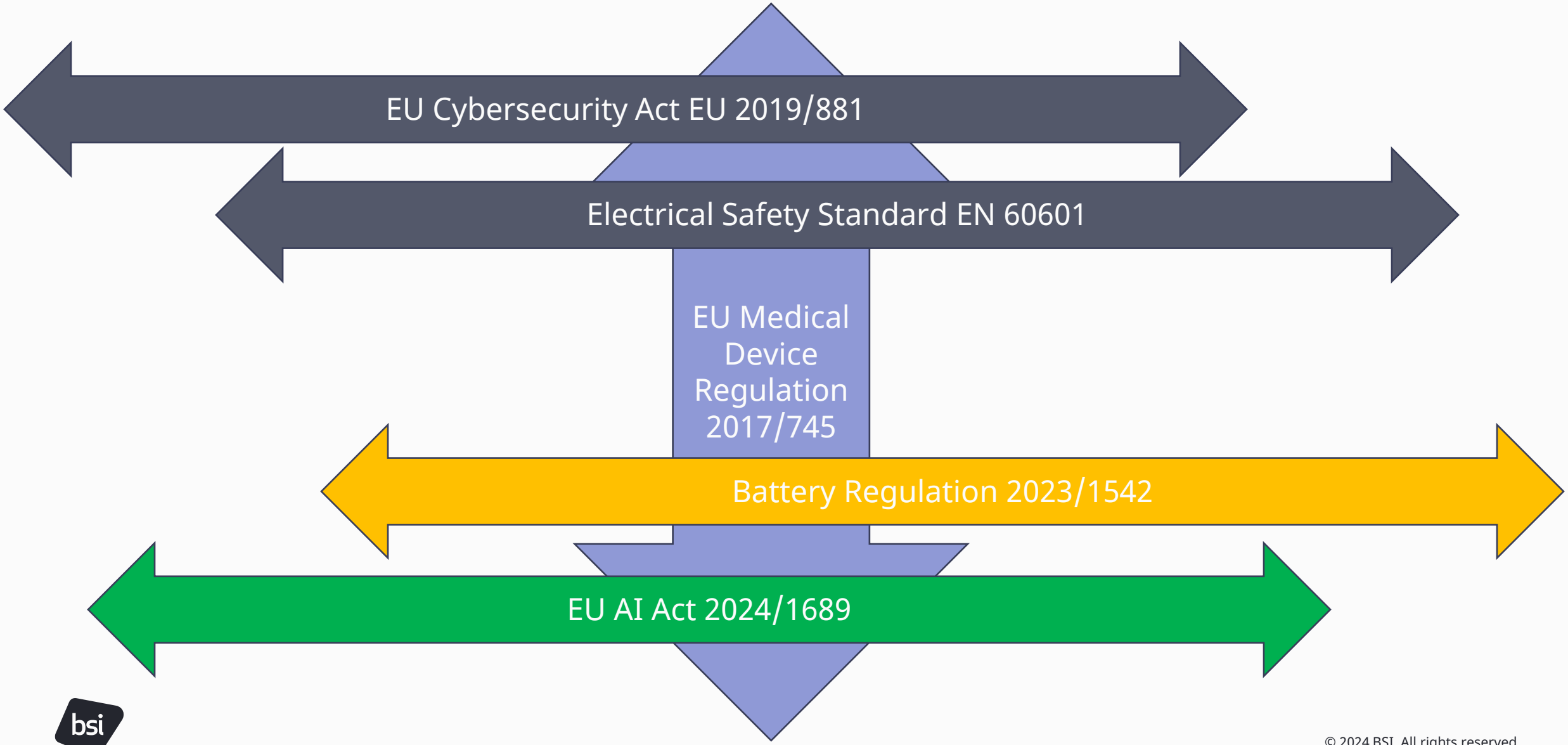
2024-11.14

Upward Trend of Software and AI based applications

- Notified Bodies are reporting significant increases in applications related to software and AI.
- Specialist Notified Bodies are being developed specifically for software as medical devices (SaMD) with services more suited to software e.g. subscription services.
- Many Notified Bodies designated under the MDR are also seeking designation under the new EU AI ACT 2024/1689 to ensure availability of AI medical devices.



Notified Body Assessment - Software



Software as a Medical Device (SaMD)

Q1: Are you a medical device?

Article 2

Definitions

For the purposes of this Regulation, the following definitions apply:

(1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

— diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,

— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,

— providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations,

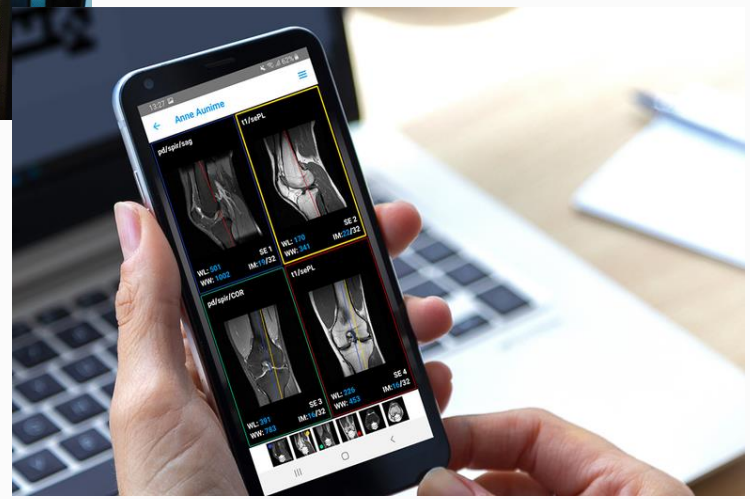
and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

- Software is specifically listed as a medical device under the EU MDR 2017/745 and EU IVDR 2017/746
- The consideration of whether the software is a medical device comes down to the intended purpose of the software and the intention of the software
- Monitoring of physiological activity not in the context of a disease would not qualify as a medical device but would rather be considered a 'wellbeing device'.
- It is also important to consider both the intended purpose and the claims of the manufacturer in relation to the software. Noting any patient management benefit.

Intended purpose of SaMD?

Q2: What is your intended purpose as SaMD?

(12) 'intended purpose' means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation;



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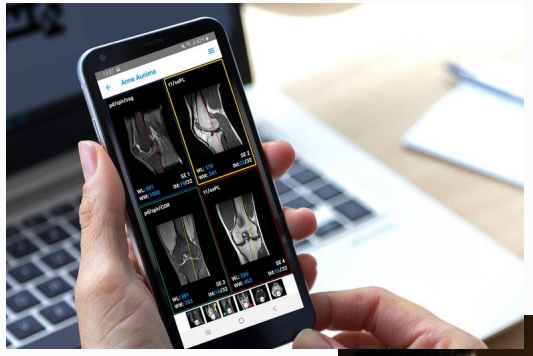
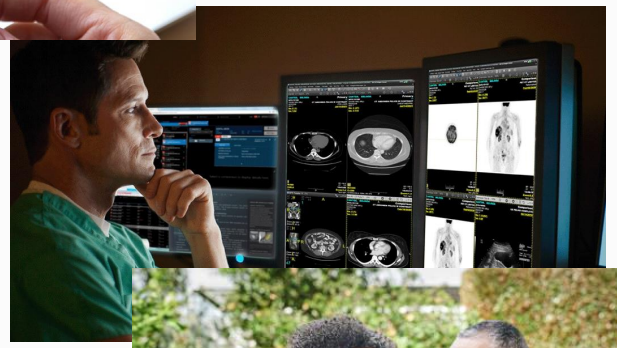
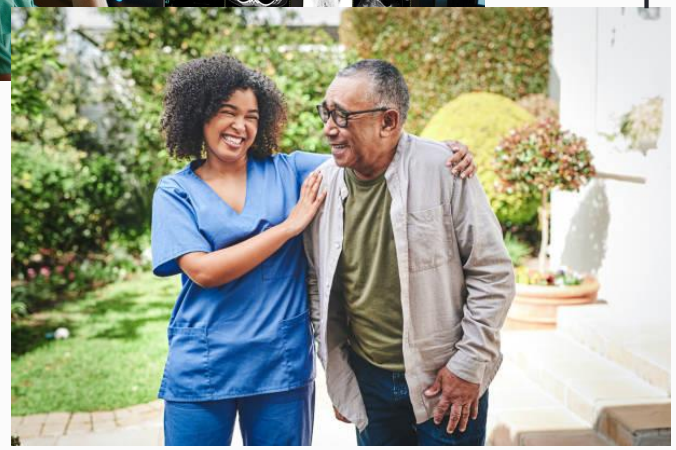


Low risk SaMD such as image display or transfer of data may be able to verify intended purpose through simulated use or ‘bench testing’ without the need for clinical data – Artcile 61 (10) of EU MDR 2017/745



Medium risk SaMD such as image manipulation or auto-diagnosis **with clinician oversight** may be supported by clinical data. These could be retrospective data sets analysed within a retrospective CI.



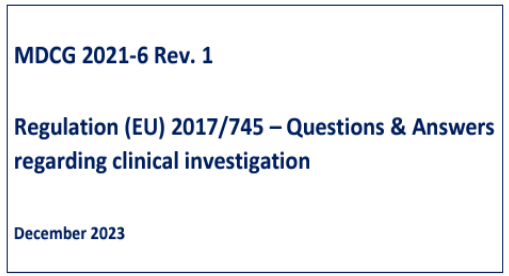
High risk SaMD such as auto decision making **without clinician oversight** or where there is a determined positive impact on patient management will require robust prospective clinical investigations.

Evidence Generation Challenges

Q3: What evidence do you have to support your clinical evaluation?

4. In the case of implantable devices and class III devices, clinical investigations shall be performed, e

- High risk SaMD (Class III) will be expected to perform clinical investigations in line with the EU MDR 2017/745.
- **Problem:** Many manufacturers using retrospective data sets which is practical but leads to concerns about the diversity of data within those data sets and the validity of this data in line with the requirments of the MDR
- MDCG 2021-6 - *If performance and/or safety of the device are analysed in the study retrospectively, separately from the decision to use the device, the study should not be considered as a clinical investigation according to the MDR,*


MDCG 2021-6 Rev. 1

Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation

December 2023

MDCG_2021-6_en.pdf

3 Important considerations when performing a Clinical Evaluation of Software (MDCG 2020-1)

- **Valid Clinical Association/ Scientific Validity**
- Important to demonstrate a good founded relationship or clinically accepted corresponding to the clinical condition, indication or parameters defined in the intended purpose.

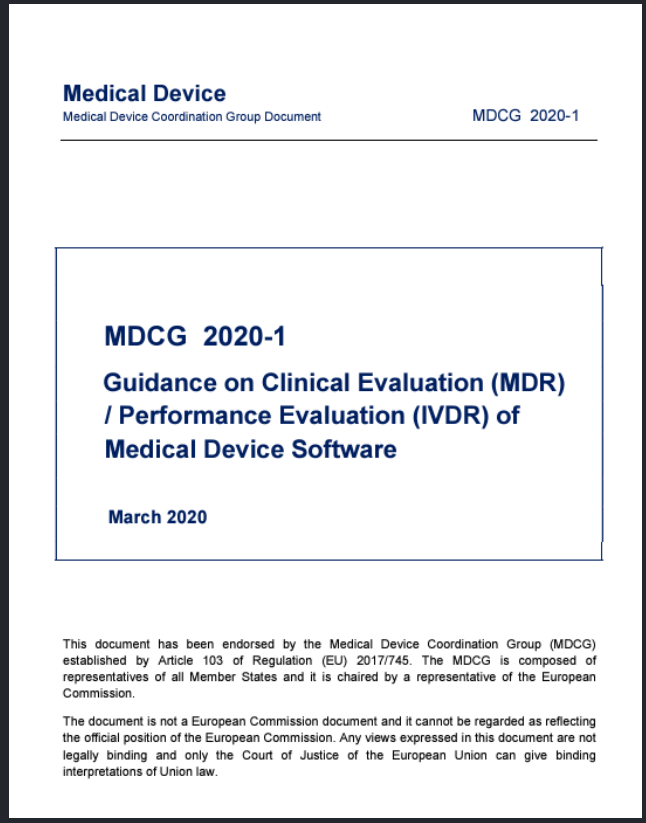
- **Technical/Analytical Performance**
- Demonstration of the MDSW's ability to accurately, reliably and precisely generate the intended output, from the input data.

- **Validation of the clinical Performance**
- Demonstration of a MDSW's ability to yield clinically relevant output in accordance with the intended purpose. The clinical relevance of a MDSW's output is a positive impact

Validation of Clinical Performance

Validation of the CLINICAL PERFORMANCE is the demonstration of a MDSW's ability to yield clinically relevant output in accordance with the intended purpose. The clinical relevance of a MDSW's output is a positive impact

- on the health of an individual expressed in terms of measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, prediction of risk, prediction of treatment response(s), or
- related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or
- on patient management or public health.



Medical Device
Medical Device Coordination Group Document MDCG 2020-1

MDCG 2020-1

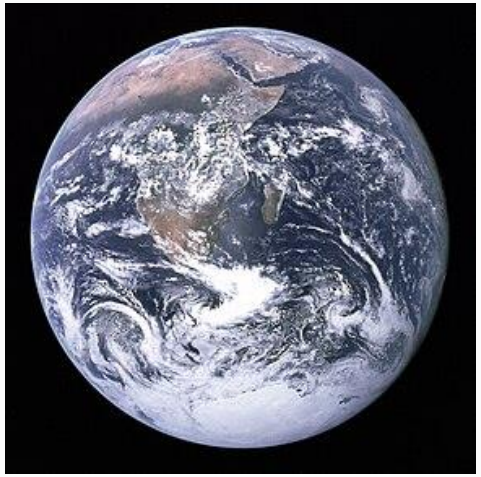
Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software

March 2020

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.

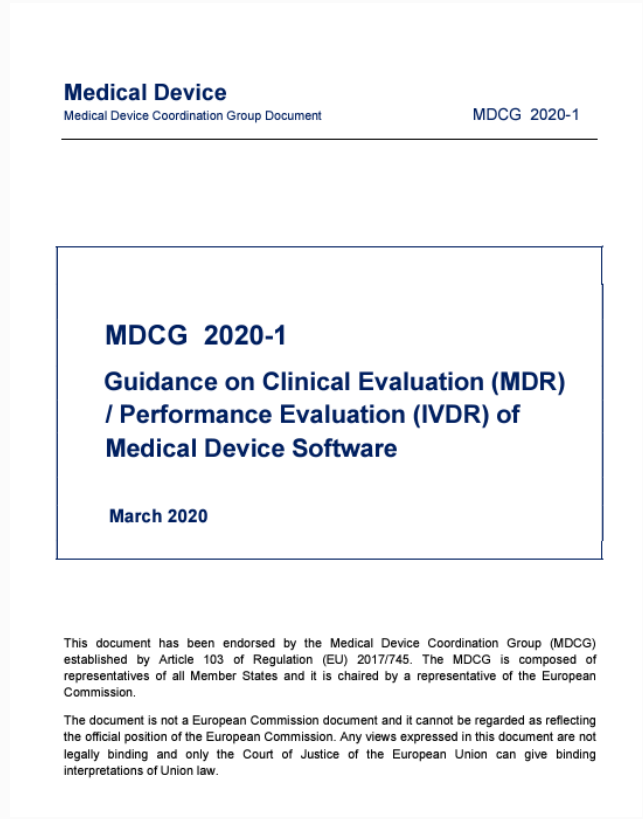
Environmental Challenges -



- There is an increasing number of software developers with limited understanding of the medical device regulations. This is leading to applications of high-risk devices without clinical data and reliance on simulated use/lab cases.
- Inexperience of start-up manufacturers is also reflected in ‘wild’ claims – e.g. determining decision for physician without substantiated evidence.
- Lack of involvement of clinicians in the development of the software .i.e. failure to determine the ‘benefit’ of the software.

Environmental Challenges -

- Lack of regulatory guidance for manufacturers and notified bodies in the clinical evaluation assessment of SaMD.
- Development and deployment of SaMD in the EU without classic '*borde*r' control.



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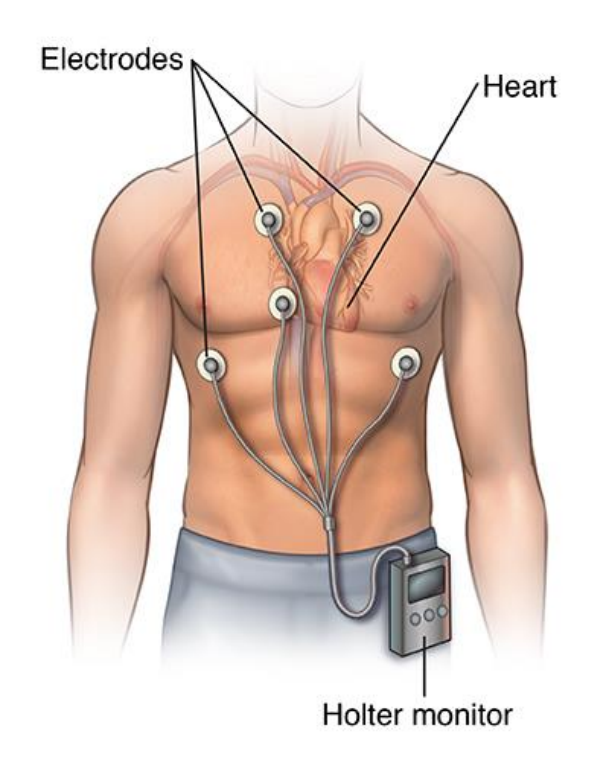
Examples

Example 1



Intended Purpose: The X Device is intended to be provide users with an awareness of their ECG during exercise. No diagnosis is provided by the device.

This device is intended to be available to users who could purchase the 6 lead device from an online retailer. Not dispensed by a healthcare professional.

Q1: Are you a medical device?

No, the device is not intending to monitor or diagnose a disease. No patient population group specified. Considered a wellbeing device.

If the device was to be used to capture symptoms with ECG recordings or provide a diagnosis or alert then it would typically qualify as medical device.

Examples

Example 2

Intended Purpose: The software is intended to provide physicians and patients with personalised medication regimes for **rheumatoid conditions, cardiovascular conditions, orthopaedic conditions and neurological conditions**.

Claims: Improvement in patient outcomes and medication compliance. .

Q1: Are you a medical device?

Yes the device is intending to provide treatment information for a disease.

Examples

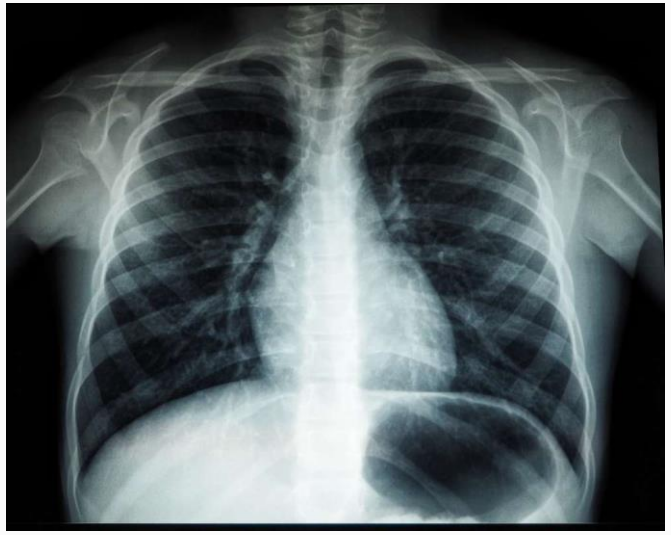
Example 2

Concerns.

- Intended purpose was very broad with no defined treatment plans or regimes to specific conditions. Manufacturer was unable to support claims and provide evidence of improved patient outcomes and compliance to medication.
- Manufacturer failed to provide evidence of validated medicinal regimes for hundreds of medical conditions.
- Prospective study would be required to demonstrate evidence of improved patient outcomes.

Examples

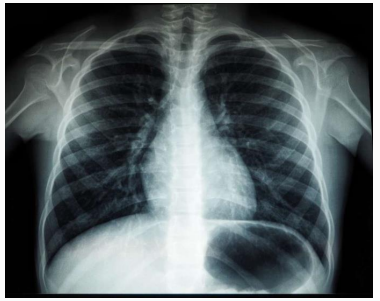
Example 3



Intended Purpose: The AI software is intended to triage chest X-Rays to determine whether there is an abnormality or not. Normal CxR are sent a report to referring physician without radiology oversight. Abnormal CXR sent to radiologist for review.

Claims: This will improve radiology departmental efficiency.

The Clinical Investigation



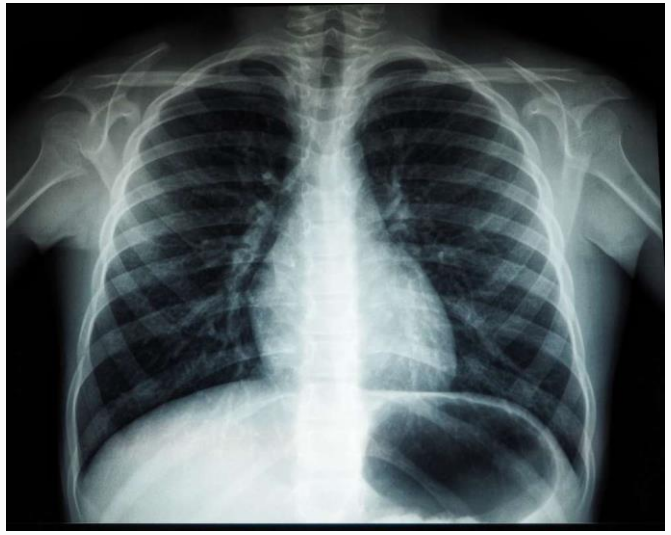
Software analysed 1000 CxR retrospectively

Two independent radiologists blindly assessed the 1000 chest X-Rays. The radiologist assessments were verified with the decision provided by the software - *agreement or disagreement*

Third radiologist provided an opinion if the 2 independent opinions differed.

Examples

Example 3



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Claims: This will improve radiology departmental efficiency.

- The software was able to accurately identify the difference between an abnormal and normal CxR and aligned to the decision of the Radiologists
- Retrospective study was accepted under the previous legislation but would be deemed not valid under MDR.
- High expectations placed in the Post Market Clinical Follow Up (PMCF) Study to ensure real world evidence supports the specificity and sensitivity claims and reflects diversity of population.
- Claim on efficiency in radiology department could not be validated, so claim was removed, but later accepted with PMCF study.

Lifecycle of Software as a Medical Device

- Medical manufacturers are required by law to report significant changes that could impact the safety or performance of a device to a notified body for evaluation and potential assessment.

- This would include updates pushed out by by iOS and Android.

Lifecycle of AI Software as a Medical Device

- As AI learns and develops from previous experience, the intended purpose may significantly change over the device lifetime.

- These changes may be unknown even by the software developers, but such a change could impact safety and performance and would need to be assessed by a notified body.

AI Act Implementation Dates

August 2024
Entry into force

6 months
Prohibited AI systems

12 months
Notifying Authorities/Notified Bodies, Obligations for GPAI, AI Governance, Penalties

24 months
All rules of the AI Act, including obligations for high-risk systems (Annex III)

36 months
Obligations for high-risk systems (Annex I)

High-risk AI Providers Requirements & Obligations

Quality management system

Risk management system

Data and data governance

Documentation keeping

Automatically generated logs

Technical documentation

Post Market Surveillance

Cooperation with competent authorities

Corrective actions & duty of information

CE Mark

EU authorised representative

Human oversight

Transparency and provision of information to deployers

Accuracy, robustness and cybersecurity

Conformity assessment

EU declaration of conformity

EU AI database registration

Accessibility requirements

Penalties of non-compliance

Member States shall lay down the rules on penalties and other enforcement measures, which may also include warnings and non-monetary measures, applicable to infringements of this Regulation by operators, and shall take all measures necessary to ensure that they are properly and effectively implemented.

€7.5m or 1.5% of AWT

An operator supplies incorrect, incomplete or misleading information to notified bodies and national competent authorities.

€15m or 3% of AWT

Failure to meet the obligations of providers, authorized representatives, importers, distributors, deployers, Notified Bodies, and transparency obligations.

€35m or 7% of AWT

Failure to comply with Article 5, which is the prohibition of certain AI systems on the EU market.

Questions?

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State of the Art

"High-risk AI systems shall comply with the requirements laid down in this Section, taking into account their intended purpose as well as the generally acknowledged state of the art on AI and AI-related technologies."

Article 8, AI Act 2024/1689