

Regulatory aspects of m-Health



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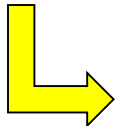
Past-Chair WG e-Cardiology 18-20

ESC Advocacy and Regulatory Affairs Committees



m-Health: a medical and public **health practice supported by mobile devices**, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices, using:

- Voice
- Short messaging service (SMS)
- 3G, 4G, 5G data-based communication
- Global positioning system (GPS)
- Bluetooth technology



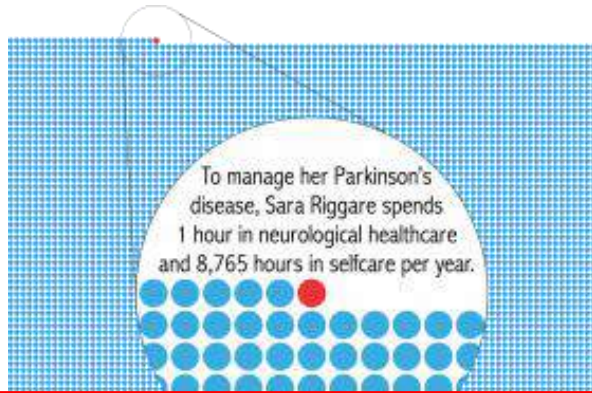
Wearables

Virtual Reality
standalone headset



[WHO. mHealth: new horizons for health through mobile, 2011].

Potential of mobile devices for healthcare



The use of **mobile devices** that allow **data collection in real time** is increasing ubiquitously, **empowering individuals** to assume a more **active role in monitoring and managing** their **chronic conditions** and therapeutic **options**, as well as their **health and**

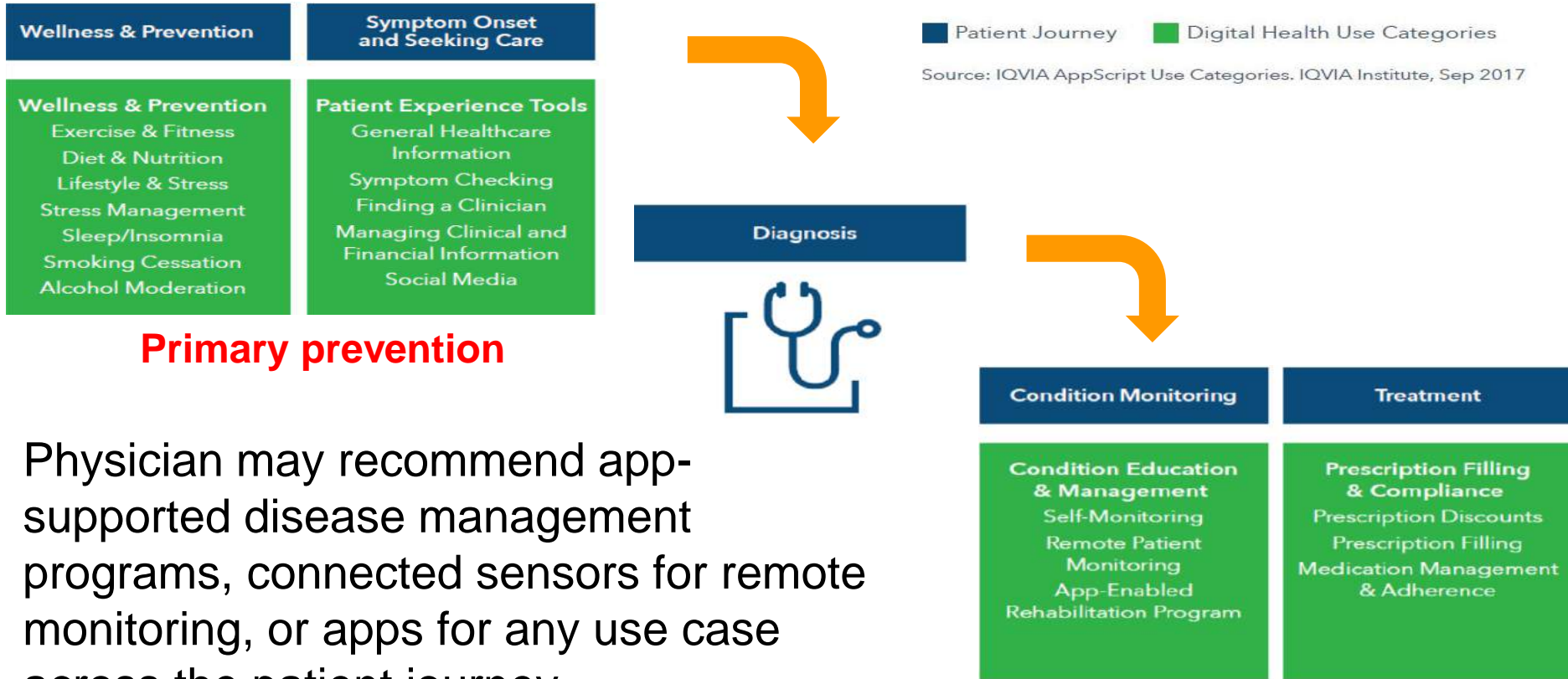
15.2 How much atrial fibrillation constitutes a mandate for therapy?

Technological advances allow screening for an irregular rhythm using patient-operated ECG devices, **smartphones**, and a variety of other technologies. These may be very useful to detect silent, unrecognised AF.¹⁵⁷ Adequately powered studies evaluating the diagnostic yield of such technologies, the diagnostic yield in different populations, the shortest duration and pattern of atrial arrhythmias conveyed, the risk, and the effect of ECG screening on outcomes are needed.
[2016 ESC Guidelines for the management of atrial fibrillation]

There is also evidence that patient self-monitoring may have a beneficial effect on medication adherence and BP control,^{60,61} especially when combined with education and counselling.⁶² **Telemonitoring and smartphone applications may offer additional advantages,^{63,64} such as an aid to memory to make BP measurements, and as a convenient way to store and review BP data in a digital diary and transmit them.** We do not recommend the use of apps as a cuff-independent means of measuring BP.

[2018 ESC/ESH Guidelines for the management of arterial hypertension]

Digital health in the patient journey



Primary prevention

Physician may recommend app-supported disease management programs, connected sensors for remote monitoring, or apps for any use case across the patient journey

Secondary prevention Digital Therapeutics

Physician's barrier

- Technology prescription

- Validity and accuracy, efficacy
- Security
- Data integrity

- Data Interpretation

- Quality of patient's acquired data?
- Automated interpretation?
- Commitment to review and interpret data (when?)

- Patient-Physician Communication

- When?
- How?
- Privacy and traceability

- Lack of reimbursement

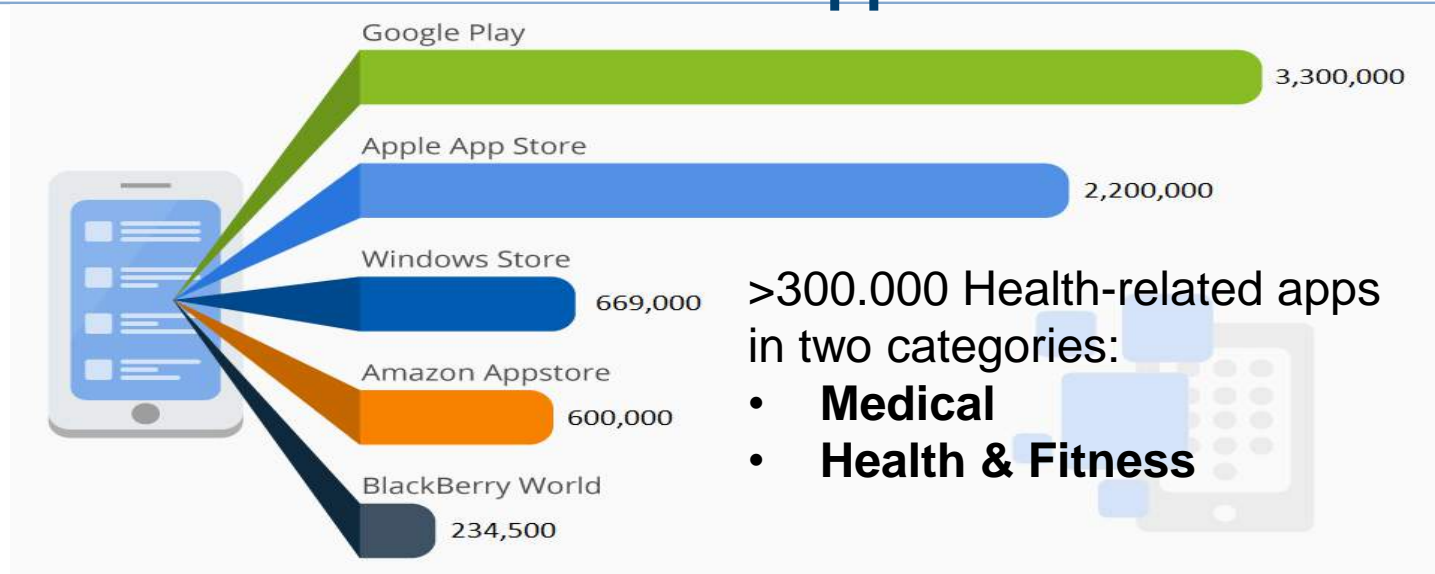
KNOW THE RULES!



Professional Liability



m-health software: health apps



It is the app developer that decides the category (primary and secondary) in which the app will be listed.

Ranking algorithms: apps "first" are the most popular, not necessarily the most valid...

What we can find in app stores



The majority of app **developers** have little or **no** formal **medical training** and do not involve physicians in the process, being **unaware of patient safety issues** due to inappropriate content [*Rodriguez MA et al, Insights Imaging 2013;4:555-62*]

Not all apps with potential medical impact are undergoing regulatory process:

- developers may be unaware of the requirements
- may be willing to avoid regulatory processes (time, money)



If you are not paying for the app, probably you are not the customer: **you and your data are the product** being sold.

m-Health component: software

Software: set of instructions that processes input data and creates output data.



Software has always been integral part of medical devices, and not considered separately from its dedicated hardware.

With the development of new digital health solutions, **software** is acquiring more and more its “own life”, being platform-independent and thus potentially acting **as medical device**.

M-health apps

Machine learning

Big Data Analytics

Cloud computing

EU and regulations for mHealth: previous attempts

10 April -10 July 2014:
public consultation on
mHealth (Green Paper)

March 2016: 20 members
of the [EU working
group](#) on mHealth.

Different stakeholders involved:

- Patients
- Healthcare professionals
- Industry
- Public authorities
- Payers and social health insurance
- Research and Academia



Conclusions

“Building these guidelines was a much more complex exercise than expected at the beginning of the process

.....

...A **minimal level of consensus** between the members of the Working Group was **not reached**. It was thus **impossible** to achieve and endorse any guidelines”

[<https://ec.europa.eu/digital-single-market/en/news/report-working-group-mhealth-assessment-guidelines>]



EU legislation on medical devices

Legislative acts about medical devices:



- Directive 93/42/EEC (MDD, **medical device**)
- Directive 90/385/EEC (AIMDD, **active implantable medical devices**)



amended by Directive 2007/47/EC



substituted by **Regulation 2017/745**
(MDR, fully in force on May 26 2020)

MEDDEV 2.1/6 (July 2016) Guidance document

Regulation: binding legislative act that must be applied in its entirety across EU

Directive: legislative act that sets out a goal that all EU countries must achieve, but it is up to the individual countries to decide how

Guidance: not binding guidelines relating to questions of application of the EU legislation

Directive 98/79/EC (IVDD, **in-vitro diagnostic medical device**) substituted in 2022 by **Regulation 2017/746 (IVDR)**

Why the new Regulation is so important?

The new EU MDR introduces new concepts, definitions, classification rules and procedural requirements for medical device software – and particularly for software products currently regulated as Class I medical devices in Europe.

Many digital health technologies will now fall into the scope of the new European MDR.

Rules apply to any SW installed/used by **users in the EU**

What is a medical device?



Art.2 (abbreviated) *Regulation 2017/745*

'**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**:

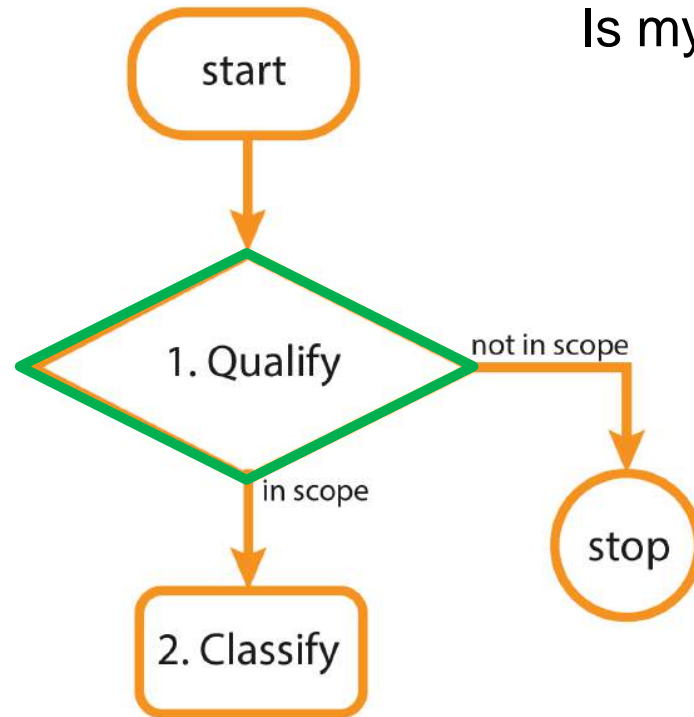
– diagnosis, prevention, monitoring, **prediction**, **prognosis**, treatment or alleviation of disease



Extension of concept of physiological data monitoring and processing with advanced digital health care technologies capable of potentially predicting or providing a prognosis of potential future states of disease identification (predictive models, risk calculators, big data analytics).

Two step process: qualification

Is my software a medical device?



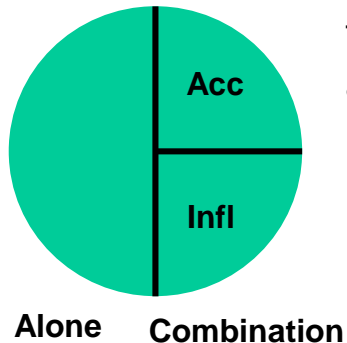
Draft MDCG 2019-XX – Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – ‘MDR’ and Regulation (EU) 2017/746 – ‘IVDR’

Definitions for qualifications

Medical Device Software (MDSW)

Medical device software is software that is intended to be used, **alone or in combination**, for a medical purpose as specified in the definition of a “medical device” in the Medical Devices Regulation.

MDSW



“**Software in its own right**, when specifically **intended by the manufacturer** to be **used for** one or more of the **medical purposes** set out in the definition of a medical device, qualifies **as a medical device**.” *Regulation 2017/745*

Software that does not meet the definition of a medical device **but** is intended by the manufacturer to be an **accessory to a medical device**, falls respectively under the scope of the MDR or IVDR.

Software that is driving or influencing the use of a medical device is covered by the MDR or IVDR either as a part/component of a device or as an accessory to a medical device.

Example: software used to operate a device (app controlling a medical device)

Other definitions that apply

Software which is intended to process, analyse, create or modify medical information can be qualified as a MDSW if the creation or modification of that information is governed by a medical intended purpose.

Example:

- image processing for findings that support a clinical hypothesis as to the diagnosis or evolution of therapy

Software for general purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes is not a medical device

Why is important to understand when software is a medical device?

For **industry/developers**:

- to avoid incurring in penalties due to false claims
- to guarantee safety, privacy, accuracy of the product
- to properly enter in certificated medical device market sector



For **physicians**:

- to avoid liability problems by using not approved software inside the hospital (cybersecurity risk)
- to be aware of the effective intended use of a software, in particular if it is recommended to a patient, or it could have an impact on the clinical decision making process.



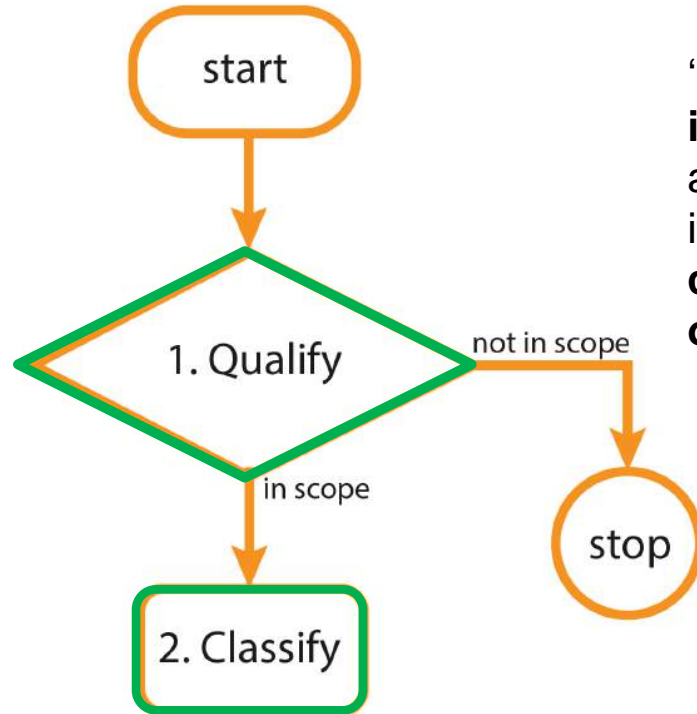
For **patients**:

- to fully understand the reliability and accuracy of what they are using, clearly distinguishing between pranks, lifestyle apps and medical devices

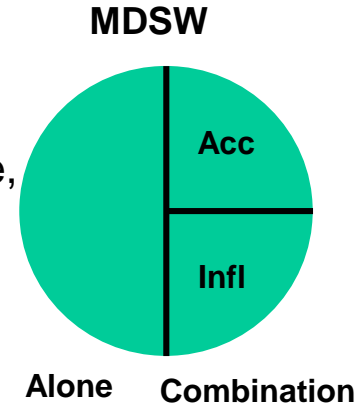


Two step process: classification

(MDR, Annex VIII, implementing Rule 3.3)



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



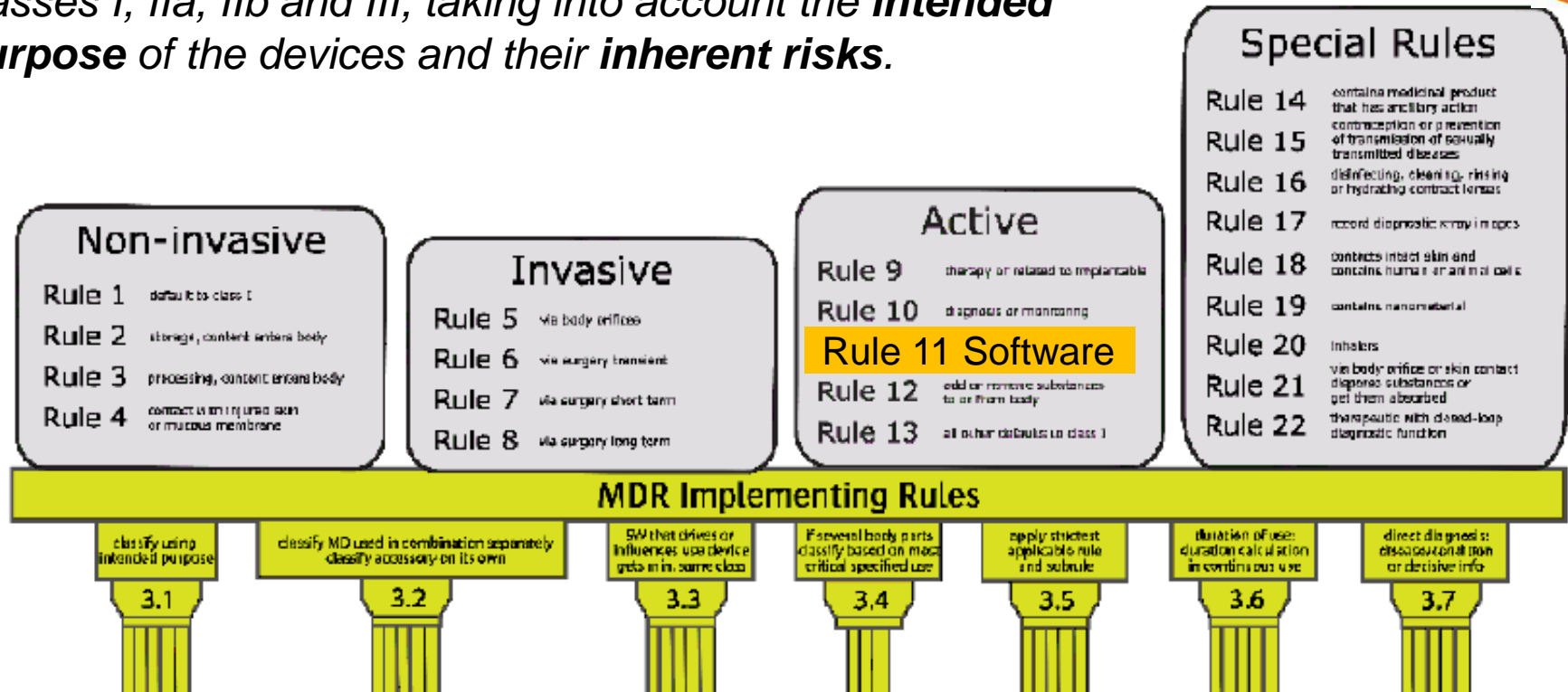
'Software, which **drives or influences** the use of a device, shall fall within the **same class as the device**'

'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**'

(MDR, Annex VIII, implementing Rule 3.5)

Classification rules

Art.51 Regulation 2017/745: Devices shall be divided into classes I, IIa, IIb and III, taking into account the **intended purpose** of the devices and their **inherent risks**.



Classification of software as medical device – Rule 11

Software intended to provide information which is used to take decisions with diagnosis or therapeutic purpose is classified as **Class IIa**, except if such decisions have an impact that may cause:

Class III: death or an irreversible deterioration of a person's state of health.

Class IIb: a serious deterioration of a person's state of health or a surgical intervention

Software intended to monitor physiological processes is classified as **Class IIa**, except if it is intended for monitoring of **vital physiological parameters**, where the **nature of variations** of those parameters is such that it could result in **immediate danger** to the patient, in which case it is classified as **Class IIb**.

Vital physiological parameters: respiration, heart rate, cerebral functions, blood gases, blood pressure and body temperature

Class I: All other medical device software.

MDR, Annex VIII, Rule 11

IMDRF classification system

Healthcare situation/ condition

Significance of Information 

	Inform clinical management	Drive clinical management	Diagnose or treat
Non-serious	IIa 1 a	IIa 1 c	IIa 2 c
Serious	IIa 1 b	IIa 2 b	IIb 3 b
Critical health condition	IIa 2 a	IIb 3 a	III 4a

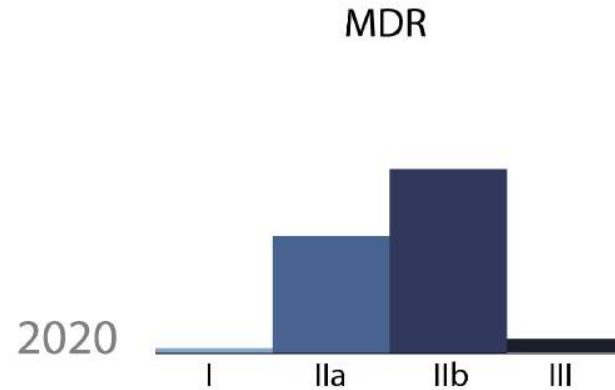
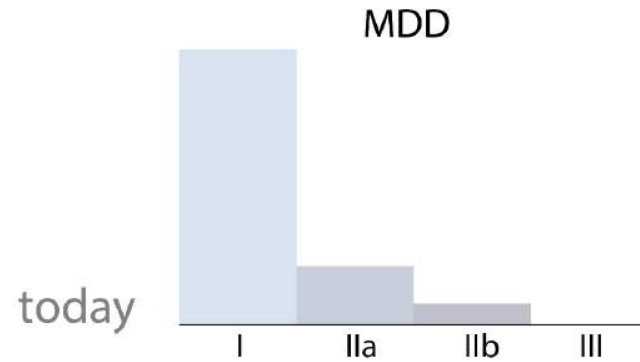
Rule 22 – Closed loop systems

Active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the device, such as closed loop systems or automated external defibrillators, are classified as **Class III**.



IMDRF International Medical Device Regulators Forum

Expected changes in classification



Expected changes in classification

MDSW intended to perform **diagnosis** by means of **image analysis** for making treatment decisions in patients with **acute stroke** should be classified as **class III** under **Rule 11(a)**

An app intended to **analyse** a user's heartbeat, **detect** abnormalities and **inform** the physician should be classified as **class IIb** per **Rule 11(a)**, if the information provided by the software is intended to guide the physician in the diagnosis.

MDSW intended to **monitor physiological processes** that are **not** considered to be **vital**, or intended to be used to obtain **readings of vital physiological signals in routine check-ups** including monitoring at home should be classified as **class IIa** for **Rule 11(b)**.

	Inform clinical management	Drive clinical management	Diagnose or treat
Non-serious	IIa 1 a	IIa 1 c	IIa 2 c
Serious	IIa 1 b	IIa 2 b	IIb 3 b
Critical health condition	IIa 2 a	IIb 3 a	III 4 a

What happens if software is a medical device?

Post-market surveillance:

- **Risk management system** to be established, implemented, documented and maintained by manufacturers of medical devices throughout the entire lifecycle, requiring systematic updating and considering also **cybersecurity** risks.
- **Unique Device Identifier (UDI)** requirements will apply also to **standalone software** (annex VI, art. 6.5) which is commercially available and constitutes medical device itself
- Inclusion in the European **database** on medical devices ('Eudamed')



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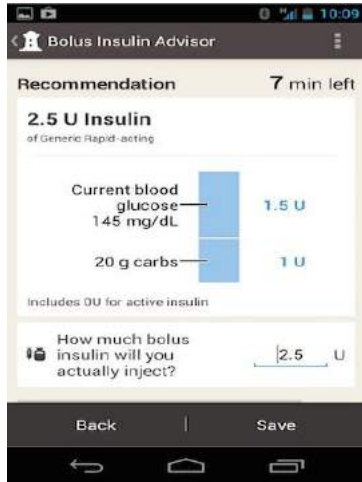
[Regulation 2017/745]

App and software recalls

“Devices that incorporate electronic programmable systems, including software, or **software** that are devices in themselves, shall be designed to ensure **repeatability, reliability and performance in line with their intended use**. In the event of a single fault condition, appropriate means shall be adopted to eliminate or reduce as far as possible consequent risks or impairment of performance. (*Annex 1*)”

- Less severe for companies than the recall of a medical device
- Due to bugs, recalls can often be quickly remedied with a patch
- Relevant to specific software versions
- Need user attention and action to be solved (update, delete the stored data, remove the app, etc.)

App and software recalls



Roche's Accu-Chek diabetes management app

15/2/18: Class 2 Device Recall for certain software versions due to a bug that could lead users to self-administer inappropriate doses of insulin.

“Due to a software bug, when the OS region of the phone setting is changed, the unit of measure within the app may unexpectedly change. This creates a risk the app might not transfer the blood glucose result or the user might not correctly input numerical values for carbohydrate used for bolus advice.”

User Interface Software Errors in Medical Devices: Study of U.S. Recall Data

Yi Zhang, Paolo Masci, Paul Jones, and Harold Thimbleby

[*Biomed Instrum Technol* 2019;53:182-94]

Software updates

“Manufacturers shall evaluate the potential impact of any changes to the function, intended use, essential design, and manufacturing characteristics on the software’s qualification as MDSW and its classification (including the classification of the combination of the MDSW with another medical device). (Annex 1)”

Screening for Atrial Fibrillation Using a Smartphone: Is There an App for That?

[J Am Heart Assoc. 2016]

Ben Freedman, MBBS, PhD

Study, Device/Algorithm, Population	n	Sensitivity	Specificity
Chan et al, ¹³ Cardiio Rhythm PPG, outpatient	1013	92.9%	97.7%
Chan et al, ¹³ AliveCor ECG, outpatient	1013	71.4%	99.4%
Lau et al, ¹⁰ AliveCor ECG, outpatient and inpatient	204	98%	97%
Lowres et al, ¹⁵ AliveCor ECG, community pharmacy	1000	98.5%	91.4%

Intentional algorithm change by the company favoring specificity over sensitivity, without informing the final user, through app upgrade.

Current EU - US regulations



Directive 93/42/EC

→ Regulation 2017/745

Regulation
2016/680 (GDPR)

Directive 2011/83/EC

**Safety and
effectiveness**

**Privacy and
security**

**Consumer
rights**



Federal Food, Drug, and
Cosmetic Act (FD&C Act)
Pre-Certification for Software

Health Insurance
Portability and
Accountability Act (HIPAA)

Federal Trade
Commission Act (FTC Act)

FDA Pre-Certification for Software

Previous FDA policy:

- **oversight** on only mobile medical apps that present **higher risk to patients**
- FDA did **not focus** oversight on technologies that receive, transmit, store or display data from medical devices (**Medical Device Data Systems**), or products that only promote **general wellness**.

What is the precertification program?

- Pre-certification for eligible digital health developers (**firm-based approach**) who demonstrate a culture of quality and organizational excellence
- Market **low-risk devices** without additional FDA review, or fast-track review.



Conclusions



The **new MDR** aims to **improving the safety** of medical devices for EU citizens, and creating the conditions to modernize the sector.

The new provisions include **changes in how software as medical device is defined**, classified in terms of risk, and subject to both pre-clinical certification and post-market evaluation, fostering high standards.

These changes go in the direction of increasing **transparency of clinical evidence for medical devices in Europe** [*Fraser A et al, Lancet 2018*]. Clinicians will feel more confident in their clinical decisions and choice of device and patient safety will be improved.



Thank you !!!



ESC

Working Group
e-Cardiology

Join us!

Clinical evaluation

benefit of MDSW may lie in providing accurate medical information on patients

Software for which the manufacturer claims a CLINICAL BENEFIT. Such software has a specific medical intended purpose and requires CLINICAL EVIDENCE within its own conformity assessment

What is CLINICAL EVIDENCE ?

“Clinical data and CLINICAL EVALUATION (MDR) / PERFORMANCE EVALUATION (IVDR) results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended CLINICAL BENEFIT(S), when used as intended by the manufacturer”.

CLINICAL EVALUATION (MDR)

A systematic and planned process to **continuously generate, collect, analyse and assess the clinical data** pertaining to a device in order to verify the safety and performance, including CLINICAL BENEFITS, of the device when used as intended by the manufacturer.

Source: EU 2017/745 (MDR), Article 2 (44)

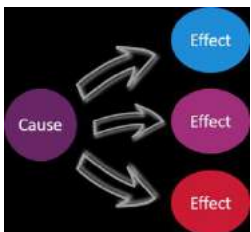
Clinical data

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;

Source: EU 2017/745 (MDR)

Three key components for clinical evidence of MDSW

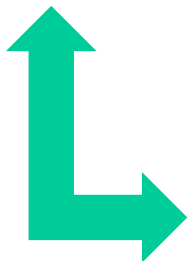


SCIENTIFIC VALIDITY/ VALID CLINICAL ASSOCIATION: The extent to which the MDSW's output (e.g. concept, conclusion, calculations), based on the inputs and algorithms selected, is associated with the targeted physiological state or clinical condition. This association should be clinically accepted or well founded (through literature research, professional guidelines, proof of concept studies, or manufacturer's own clinical studies/clinical performance studies)

ANALYTICAL / TECHNICAL VALIDATION: Demonstration of the ability of a MDSW to accurately, reliably and precisely generate the intended output, from the input data (through verification and validation activities, e.g. unit-level, integration, and system testing or by generating new evidence through use of curated databases or use of previously collected patient data).

Three key components for clinical evidence of MDSW

CLINICAL VALIDATION: Demonstration of a MDSW's ability to yield clinically meaningful output, in accordance with the intended purpose.



demonstrated predictable and reliable use
and **USABILITY**

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);
- on the device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients,
- on patient management or on public health

FDA Pre-Certification for Software

Previous policy:

- FDA focused **oversight** on mobile medical apps to only those that present **higher risk to patients**, while choosing not to enforce compliance for lower risk mobile apps;
- FDA did **not focus** oversight on technologies that receive, transmit, store or display data from medical devices (**Medical Device Data Systems**);
- FDA did **not focus** oversight on products that only promote **general wellness**.

Under the 21st Century Cures Act (Dec 2016), certain medical software, including certain software that supports administrative functions, encourages a healthy lifestyle, serves as electronic patient records, assists in displaying or storing data, or provides limited clinical decision support, is no longer considered to be and regulated as a medical device.

FDA Pre-Certification for Software

Why this program? Traditional implementation of the premarket requirements may impede or delay patient access to critical evolutions of software technology, particularly those presenting a lower risk to patients.

What is the precertification program?

It is a **firm-based approach** that could replace the need for a premarket submission for certain products and allow for decreased submission content and/or faster review of the marketing submission for other products.

How does it work?

CDRH could “pre-certify” eligible digital health developers who demonstrate a culture of quality and organizational excellence based on objective criteria. Pre-certified developers could then qualify to be able to market their lower-risk devices without additional FDA review or with a more streamlined premarket review.



Based on 5 Excellence Principles

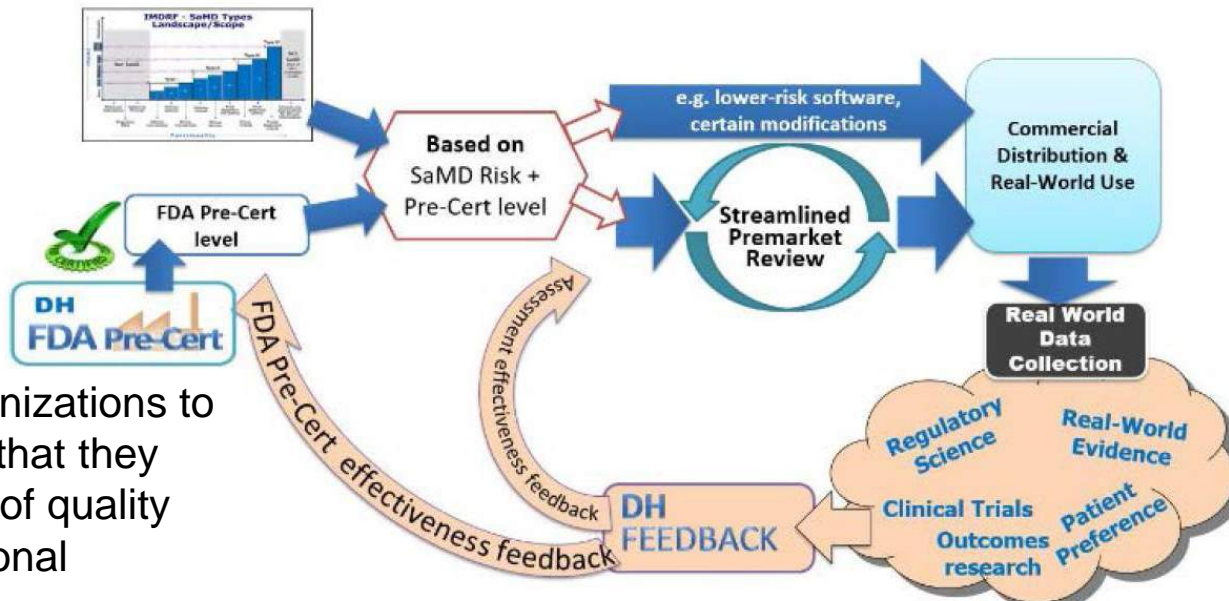
 Patient Safety	Demonstration of a commitment to providing a safe patient experience , and emphasizing patient safety as a critical factor in all decision-making processes.
 Product Quality	Demonstration of a commitment to the development, testing, and maintenance necessary to deliver Software as a Medical Device (SaMD) products at the highest level of quality .
 Clinical Responsibility	Demonstration of a commitment to responsibly conduct clinical evaluation and ensure that patient-centric issues including labeling and human factors are appropriately addressed.
 Cybersecurity Responsibility	Demonstration of a commitment to protect cybersecurity , and proactively address cybersecurity issues through active engagement with stakeholders and peers.
 Proactive Culture	Demonstration of a commitment to a proactive approach to surveillance, assessment of user needs, and continuous learning.

FDA Pre-Certification for Software

Concept: A Reimagined Approach



An organization-based streamlined regulatory approach for Software as a Medical Device (SaMD) that relies on a demonstrated culture of quality and organizational excellence

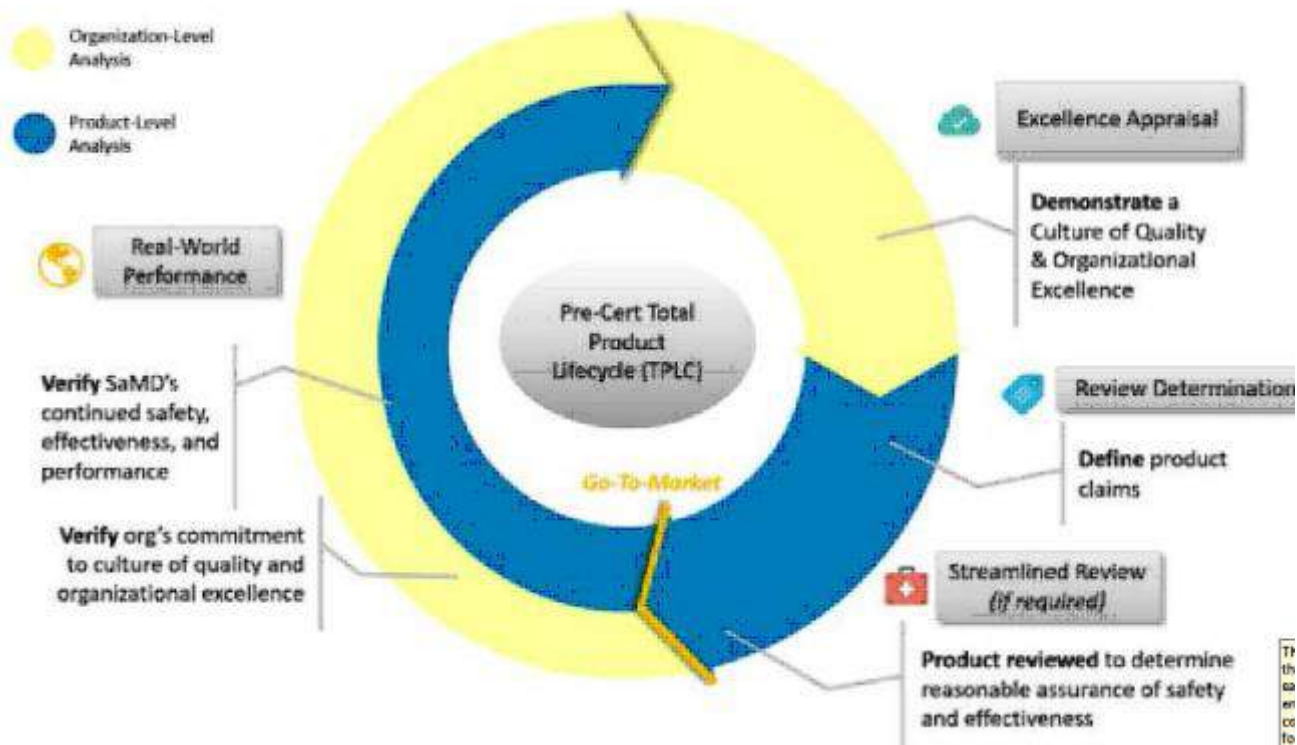


Assesses organizations to establish trust that they have a culture of quality and organizational excellence

Leverage unique postmarket opportunities to **verify** continued safety, effectiveness, and performance

Leverage transparency

FDA Pre-Certification for Software



FDA Pre-Certification for Software



Nine companies selected:

Apple

Fitbit

Johnson & Johnson

Pear Therapeutics

Phosphorus

Roche

Samsung

Tidepool

Verily

2019 Test Approach

