Clinical evaluation of MDSW

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Medical device software (MDSW)

MDSW 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 medical devices regulation or in vitro diagnostic devices regulation.

MDCG 2019-11

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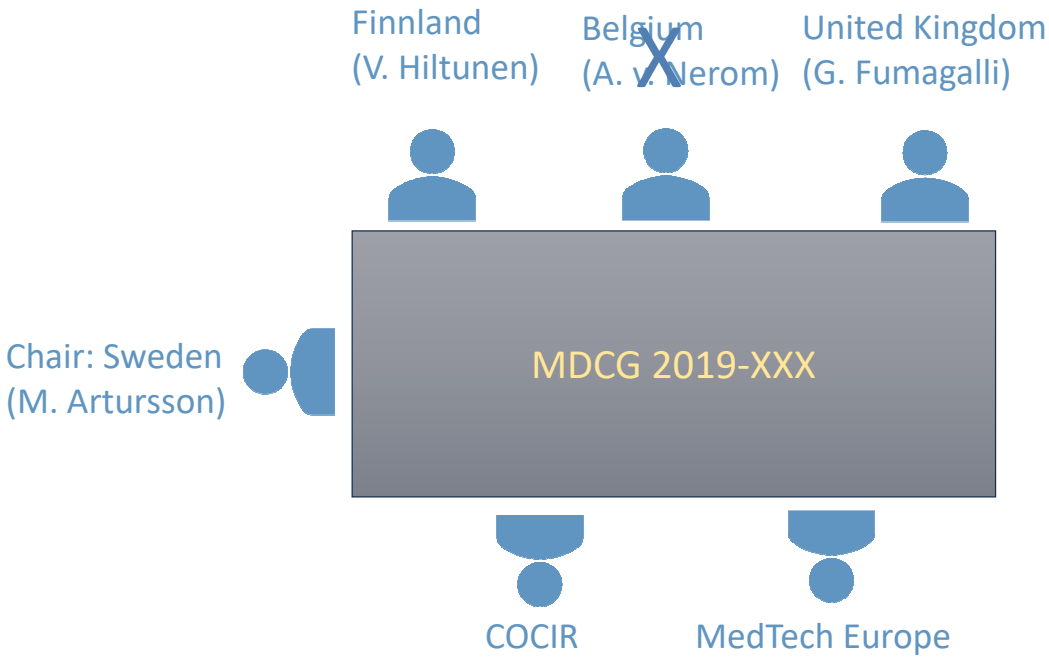
Unique challenges of MDSW

- Deployed on a multitude of technology platforms
- Failures are almost always caused by design errors but code development is usually opaque to most members of design review team
- Interconnected to other systems and datasets
- Rapid development cycles, frequent changes
- Duplicated in numerous copies and widely spread (outside the control of the manufacturer)

Task force: Clinical evaluation for MDSW



- Describe methodological principles for performing clinical evaluation of MDSW (MDR and IVDR)
- Provide guidance on how to determine sufficient level of clinical evidence for MDSW
- Harmonize terminology and understanding of IMDRF N41 under the EU legislative framework and existing guidance (MEDDEV 2.7/1 rev 4)

Supporting Members:

- TeamNB / TÜV Süd (A. Hoeppner, H.H. Junker)
- United Kingdom (D. Grainger, C. Fleetcroft)

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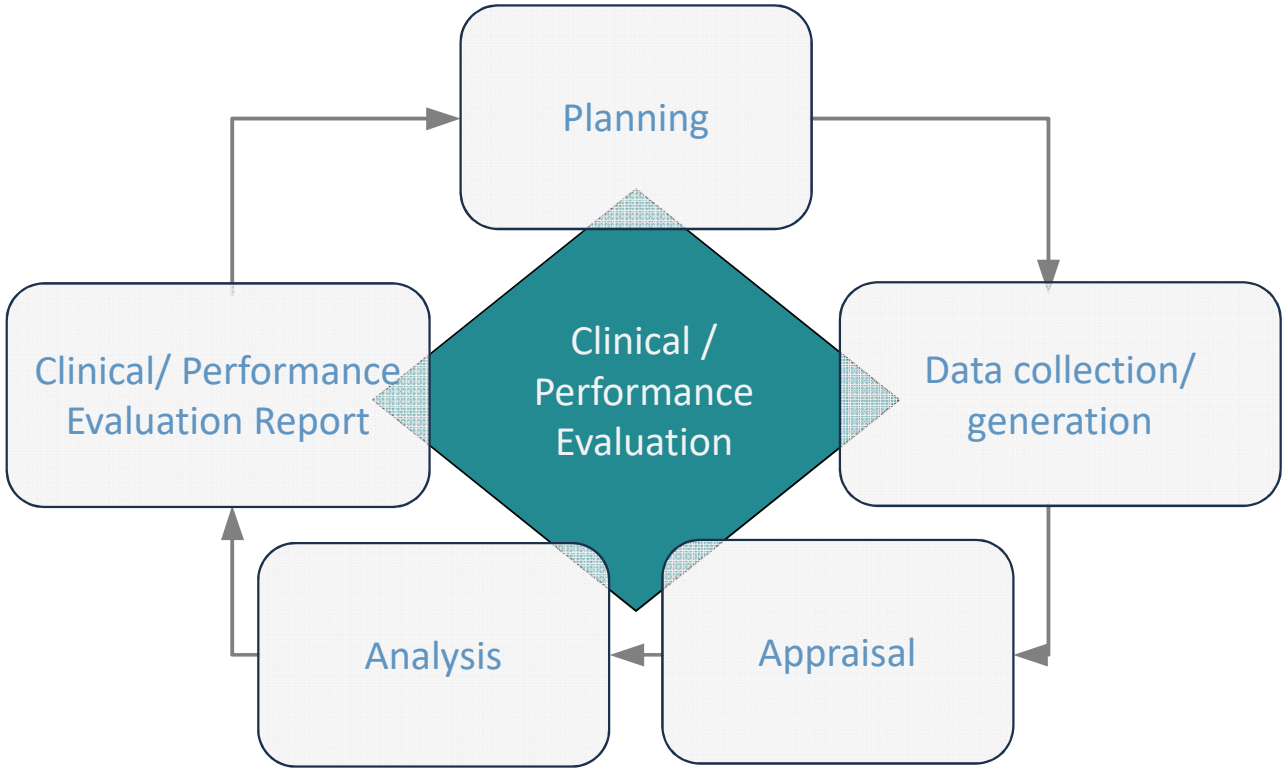
General principles of clinical evaluation



Aim:
Demonstration of conformity with relevant GSRPs under the normal conditions of the intended use of the device.

Process characteristics:

Continuous

Structured, transparent, iterative

Similar principles for MDSW under MDR and IVDR

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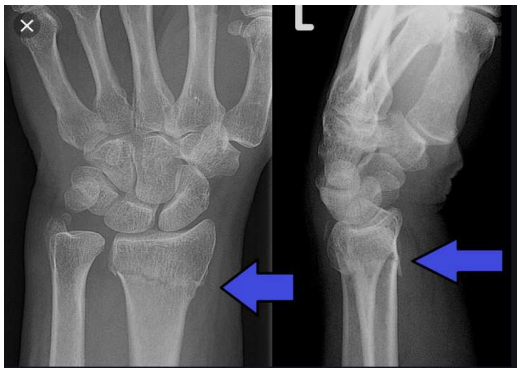
Planning of clinical evaluation

Model of software



Independent medical purpose
AI-driven software intended to detect signs of distal radius fracture on X-ray images

Drives or influences a medical device for a medical purpose
Closed loop insulin delivery system

Software driving or influencing the use of a medical device (component/accessory)
Software that encrypts data for transmission from a medical device.

Clinical evaluation scope

MDSW only	MDSW and the driven or influenced medical device	Driven or influenced medical device including the software (component or accessory)

Planning of clinical evaluation

MDR Annex XIV, Part A: Clinical Evaluation Plan

Intended purpose

Applicable GSPRs

Target group

Indication(s) and contraindication(s)

Clinical benefit

Methods to examine clinical safety and determine residual risks & side effects

Parameters to determine acceptability of residual risk and side effects according state of the art

Risk/benefit relating to specific components

To consider

Level of dependence or reliance by the user upon the output information; Autonomy

Type of interaction with a human body

Transparency of the inputs, outputs and methods to the user

Ability of the user to detect an erroneous output information

Maturity of clinical basis of the software and confidence in the output

Technological characteristics of the platform the software are intended to operate on

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Clinical data requirements

At minimum

GSPR 1

- Safety
- Clinical perfromance
- Acceptable benefit-risk profile

GSPR 5

- Use error

GSPR 6

- Perfromance and safety over device's lifetime

GSPR 8

- Acceptability of undesirable side-effects

….. where the demonstration of conformity with GSPRs based on clinical data is not deemed appropriate, adequate justification for any such exception shall be given based on the results of

- the manufacturer's risk management,
- on consideration of the specifics of the interaction between the device and the human body,
- the clinical performance intended, and
- the claims of the manufacturer.

In such a case, the manufacturer shall duly substantiate in the technical documentation why it considers a demonstration of conformity with GSPRs that is based on the results of non-clinical testing methods alone, including performance evaluation, bench testing and preclinical evaluation, to be adequate.

MDR Annex XIV

Clinical evidence for MDSW

Valid Clinical Association / Scientific Validity

- 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

Analytical /Technical Validation

- Demonstration of the ability of a MDSW to accurately, reliably and precisely generate the intended output, from the input data

Clinical Validation

- Demonstration of a MDSW's ability to yield clinically meaningful output in accordance with the intended purpose.

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Scientific Validity

The association should be clinically accepted or well founded, → accepted by the broad medical community and/or described in the peer-reviewed scientific journals.

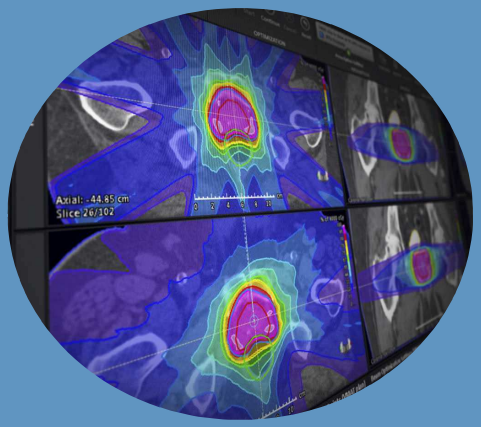
Each clinical feature governed by the intended purpose require individual assessment

Can be demonstrated through the use of existing data while taking into account the generally acknowledge state-of-the art

KIDNEY DISEASE POC ANALYZER

Creatinine as a well-established biochemical marker for renal function

RT TREATMENT PLANNING SYSTEM



Applying a validated method for dose calculation

Generation of new clinical / performance data where existing data is not sufficient

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Analytical / technical validation

Performance characteristics linked to the analytical and / or clinical features, should be supported by evidence generated during V&V activities (IEC 62304) or by generating new evidence if gaps are identified.

Objective evidence that the MDSW specifications conform to user needs and intended uses, and that the particular requirements implemented can be consistently fulfilled.

Performance verification

- accuracy (resulting from trueness and precision)
- limit of detection
- limit of quantitation
- analytical specificity
- linearity
- cut-off value(s) (ISO 18113-1:2009 A.3.13)
- measuring interval (range)

Performance validation

- expected data rate or quality,
- connectivity (remote networks, COTS consumer electronics)
- known cybersecurity vulnerabilities
- Usability (human factor engineering)

Clinical validation

Generating evidence to demonstrate that MDSW generate clinically meaningful output in accordance with the intended purpose

Clinically meaningful= positive impact of the device…

…on the health of individual - measurable patient outcome(s)
(MD)

…related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients
(IVD)

…patient management or public health
(MD & IVD)

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Clinical validation

During clinical validation the manufacturer should demonstrate that:

- the MDSW has been tested for the intended use~~(s), target population(s)~~, use condition(s), operating- and use environment(s) and with all intended user group(s)

Tool-type MDSW

~~Clinical investigation, Clinical perfromance study~~, Clinical usability

- users can achieve clinically meaningful outputs, through predictable and reliable use of the MDSW

Verification & Validation
(IEC 62304, IEC 82304, IEC 62366)

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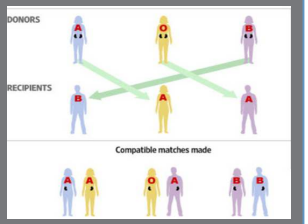
Clinical validation

Positive impact on the health of an individual, → measurable, patient-relevant clinical outcome(s)

Knee navigation application for computer-assisted knee surgery

Positive impact related to its function (screening, monitoring, diagnosis or aid to diagnosis)

Electronic system for matchng donors with organ receipients



Positive impact on patient management or public health

Medical imaging processing software

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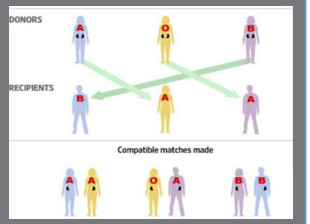
Clinical validation

Positive impact on the health of an individual, → measurable, patient-relevant clinical outcome(s)

- RCT with outcome-related endpoints measures
- Clinical usability / user interface

Positive impact related to its function (screening, monitoring, diagnosis or aid to diagnosis)

Electronic system for matchng donors with organ receipients



Positive impact on patient management or public health

Medical imaging processing software

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Clinical validation

Positive impact on the health of an individual, → measurable, patient-relevant clinical outcome(s)

- RCT with outcome-related endpoints measures
- Clinical usability / user interface

Positive impact related to its function (screening, monitoring, diagnosis or aid to diagnosis)

- Clinical performance study with outcomes related to clinical performance claims (e.g. sensitivity, specificity)
- Clinical usability / user interface

Positive impact on patient management or public health

Medical imaging processing software

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Clinical validation

Positive impact on the health of an individual, → measurable, patient-relevant clinical outcome(s)	• RCT with outcome-related endpoints measures • Clinical usability / user interface
Positive impact related to its function (screening, monitoring, diagnosis or aid to diagnosis)	• Clinical performance study with outcomes related to clinical performance claims (e.g. sensitivity, specificity) • Clinical usability / user interface
Positive impact on patient management or public health	• Clinical usability / user interface

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Sufficient clinical evidence?

Sufficient amount	Sufficient quality
▪ Intended use	▪ Type and design of study/test
▪ All indications	▪ Type of data sets
▪ All target groups	▪ Actuality of data set
▪ Clinical claims	▪ Statistical evidence, power , etc.
▪ Safety (risks)	▪ Ethical considerations
▪ Performance	▪ Quality, Monitoring
▪ Contra indication	▪ Legal/Regulatory considerations
▪ Grade of innovation	▪ State of the art
▪ Interconnection, data input and output	▪ Conflict of interest

Oxford CEBM Levels of Evidence

Applicable Standards

ISO14155
IEC 62366
ISO 20916
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Clinical investigations/ performance studies

For MDSW, with no claims related to patient outcomes or patients management, retrospective studies may contribute to the body of clinical evaluation pre-market.

Requires adequate access to data sets of sufficient amount and quality and obtained from the target population

- Diagnostic value of investigational images compared to the diagnostic value of predicate images as assessed by a radiologist

Comparison of the number of readmissions predicted to the number actually observed for the performance evaluation of the prediction algorithm

Validation of the algorithmic blood analysis software with the previously collected blood samples

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Clinical investigations/ performance studies

FDIS SO 14155:2019

Regulatory status	PRE MARKET		POST MARKET	
Clinical development stage	Pilot stage (I.3.1)	Pivotal stage (I.3.2)	Post market stage (I.3.3)	
Type of design	Exploratory or confirmatory (I.4.1)	Confirmatory (I.4.2)		
Descriptors of clinical investigations	First in human (I.5.1) Early feasibility (I.5.2) Traditional feasibility (I.5.3)	Pivotal clinical investigation (I.5.4)	Post market clinical investigation (I.2.2)	Post market clinical investigation (I.2.2)
Burden to subject	Interventional (I.6.1)		Interventional (I.6.1)	Non-Interventional (I.6.2)

"For **SaMD**, the standard applies as far as relevant."

Exemptions based on the uniqueness of indirect contact between subjects and the SaMD

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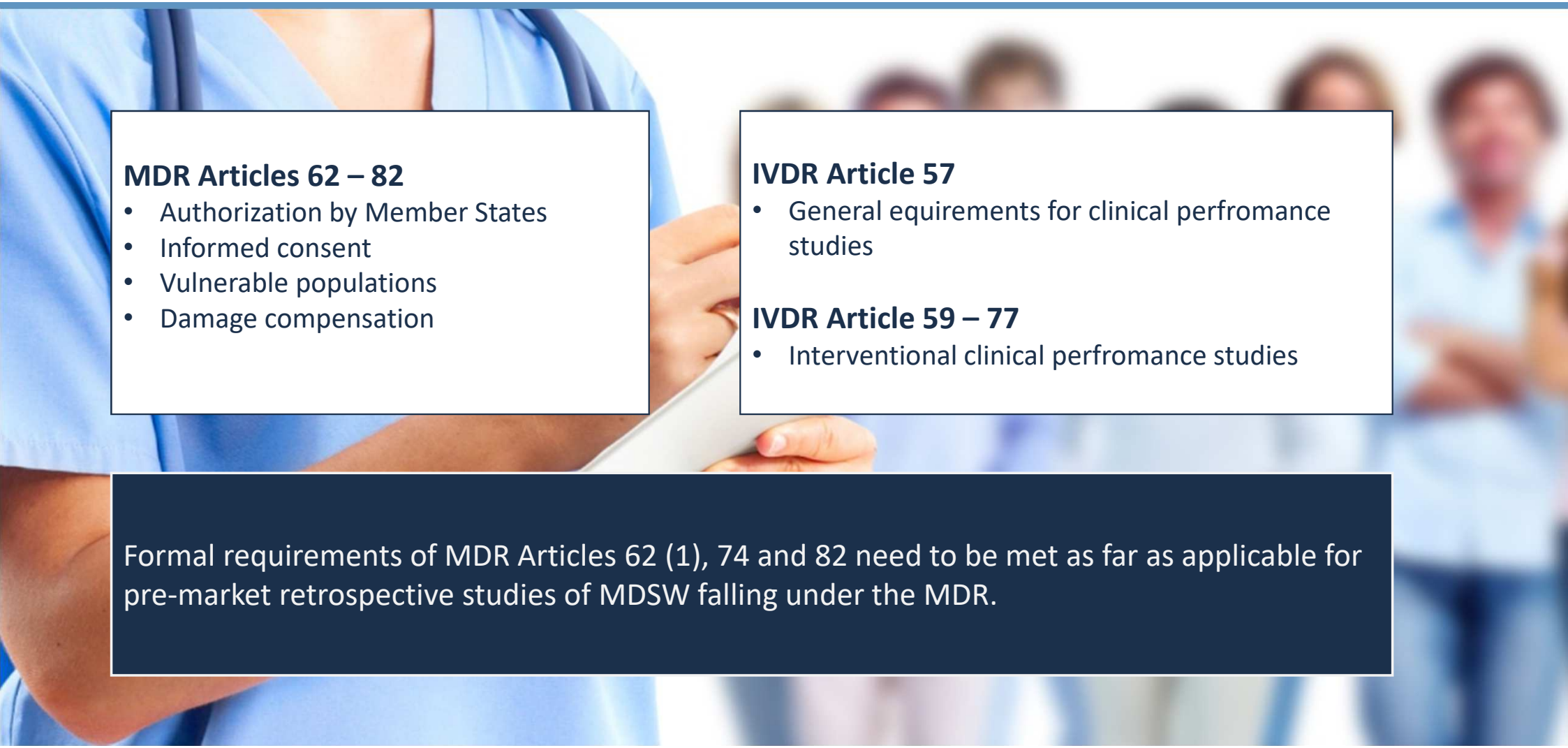
Clinical investigations/ performance studies



MDR Articles 62 – 82

- Authorization by Member States
- Informed consent
- Vulnerable populations
- Damage compensation

IVDR Article 57

- General equirements for clinical perfromance studies

IVDR Article 59 – 77

- Interventional clinical perfromance studies

Formal requirements of MDR Articles 62 (1), 74 and 82 need to be met as far as applicable for pre-market retrospective studies of MDSW falling under the MDR.

Machine Learning MDSW

Scientific validation

- Rapid evolution –specific technologies, techniques, algorithms, models or toolsets obsolete in a short period of time
- Validity of scientific knowledge deduced from performance metrics (clinical validation)
- Evaluation of the appropriateness of the algorithm used

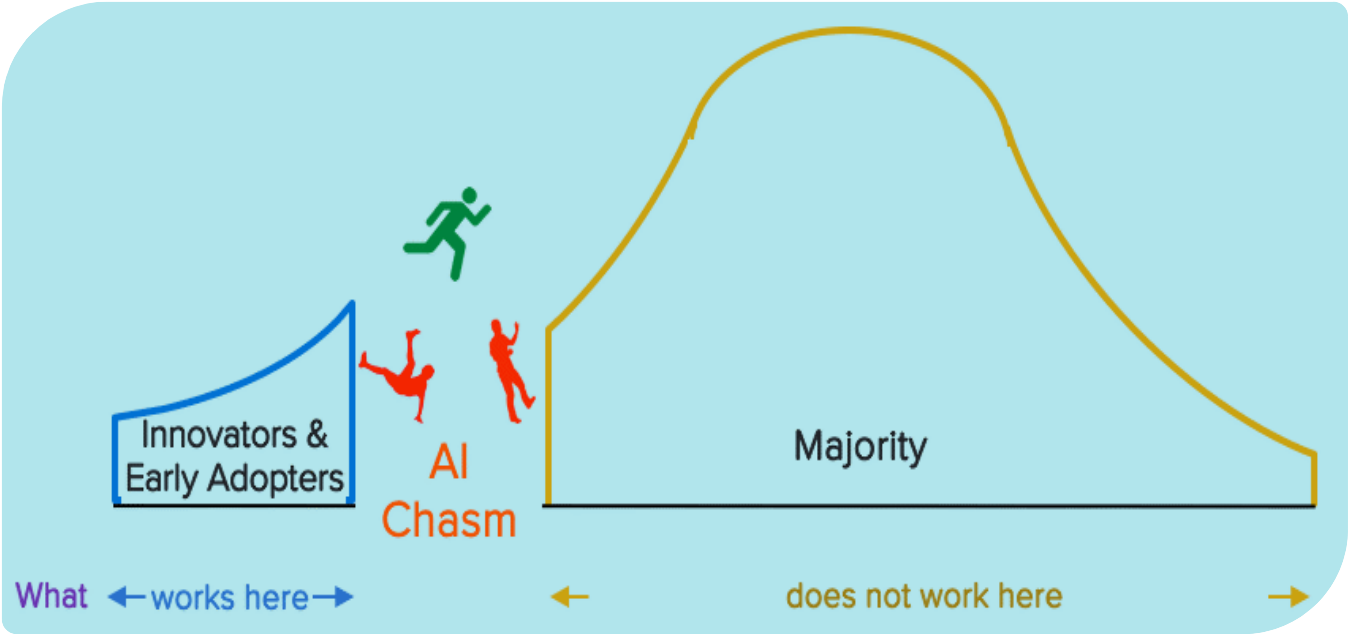
Analytical validation

- Detection of anomalies and/or elimination of errors

Clinical validation

- Measurement of the performance of the AI system by using an independent reference standard

Machine Learning MDSW



Algorithm with an AUC of 0.99 may not be adapted in the clinical practice

Manufacturers should consider a clear demonstration that when the solution is integrated into the clinical decision-making process, it helps the clinical team do a better job.

In general, the less interpretable the model, the higher level of evidence should be provided.

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Thank you

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