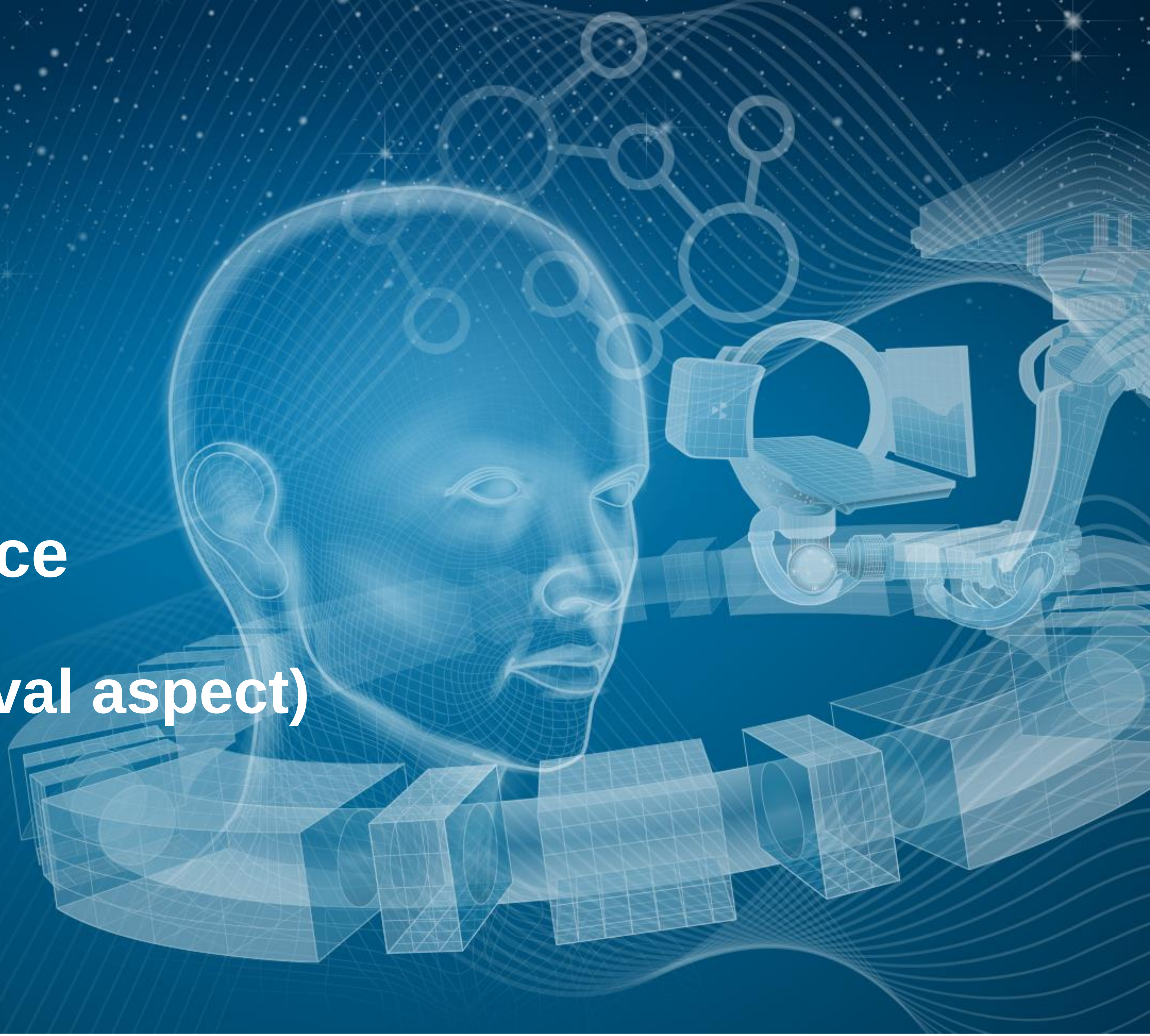
SaMD

Risk Management,
Clinical Evaluation,
Post-Market Surveillance

(part of regulatory approval aspect)



Dr. Rok Hrovatin, COSYLAB
25/03/2021

The Three Pillars

Risk management

Summary of safety
Hazard, harm,
severity, probability, risk
Risk control,
Benefit / risk,
Usability
Side effects, warnings
Contraindications
Cyber security

Post-Market Surveillance

Own device:

- Complaint handling, PMCF,
  adverse events, recalls,
  Feedback, trends,
  customer notificatons, studies

Similar devices:

- adverse events, recalls,
  market trends, studies

Clinical evaluation

Summary of performance

- Technical performance
- Clinical performance
- Scientific validity

Safety …

… freedom from unacceptable risk.

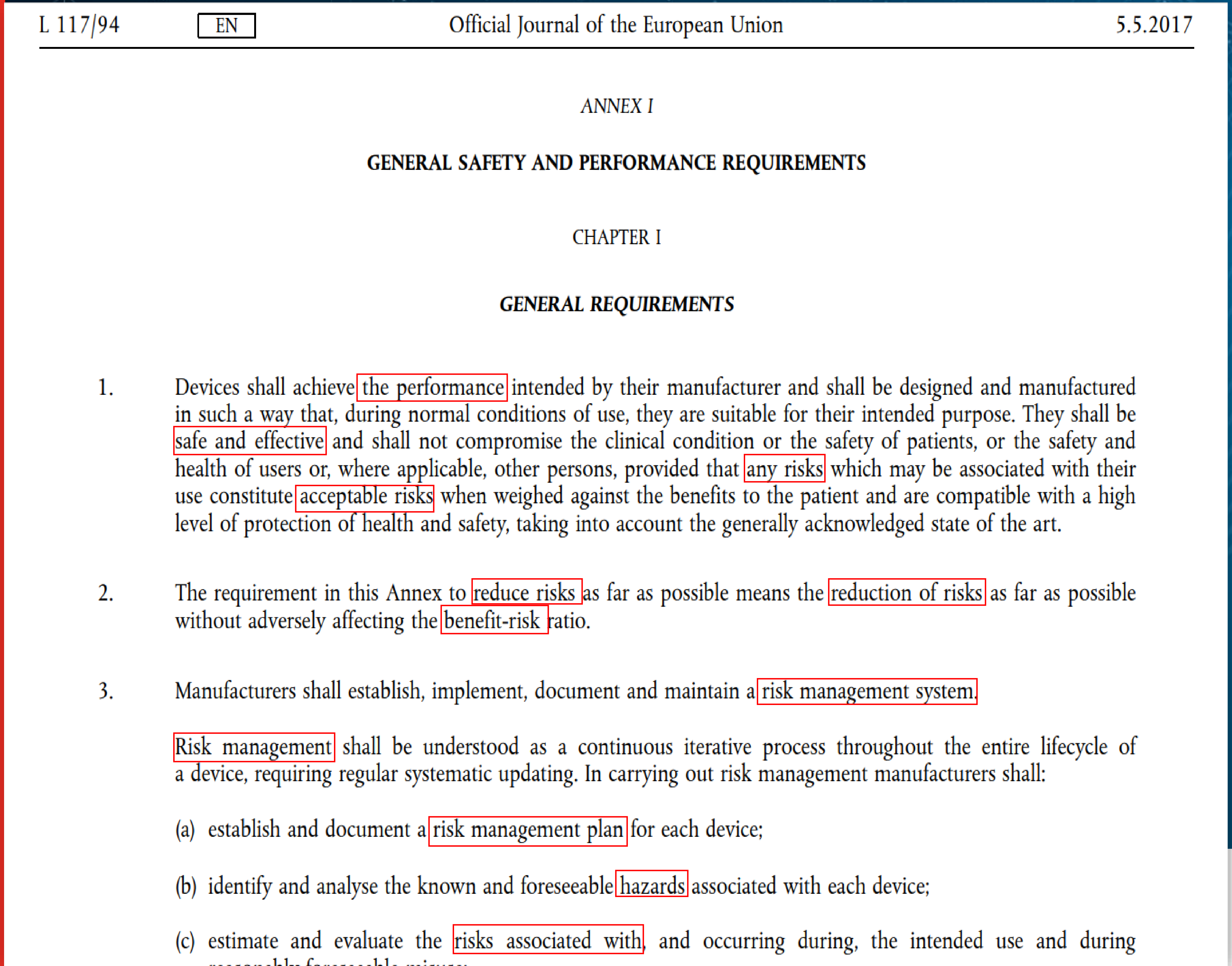
Classification of all medical devices is risk based – the higher the class, the higher the risk

Rule 11 Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:
— death or an irreversible deterioration of a person's state of health, in which case it is in class III; or
— a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.

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.

All other software is classified as class I.

Risk (and performance) related requirement(s)



L 117/94 EN Official Journal of the European Union 5.5.2017

ANNEX I

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

CHAPTER I

GENERAL REQUIREMENTS

1. Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.

2. The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.

3. Manufacturers shall establish, implement, document and maintain a risk management system.

Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall:

(a) establish and document a risk management plan for each device;

(b) identify and analyse the known and foreseeable hazards associated with each device;

(c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse;

- One of the key requirements of the GSPR (General Safety and Performance Requirements): Initial General Requirements
- Repeated along anumber of points
- Addressed in relation to products as well as to processes
- Clear requirement for a Risk management system
- Specific requirements for „medical software“ – as part of medical device or SaMD

MDR: Requirements for SW

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

REQUIREMENTS REGARDING DESIGN AND MANUFACTURE

14.2. Devices shall be designed and manufactured in such a way as to remove or reduce as far as possible the risks associated with the possible negative interaction between software and the IT environment within which it operates and interacts.

17. Electronic programmable systems — devices that incorporate electronic programmable systems and software that are devices in themselves

17.1. 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.

17.2. For devices that incorporate software or for software that are devices in themselves, the software shall be developed and manufactured 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.

17.3. Software referred to in this Section that is intended to be used in combination with mobile computing platforms shall be designed and manufactured taking into account the **specific features** of the mobile platform (e.g. size and contrast ratio of the screen) and the external factors related to their use (varying environment as regards level of light or noise).

17.4. Manufacturers shall set out **minimum requirements** concerning hardware, IT networks characteristics and IT **security measures**, including protection against unauthorised access, necessary to run the software as intended.

MDR: Requirements for SW (2)

GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

REQUIREMENTS REGARDING THE INFORMATION SUPPLIED WITH THE DEVICE

23.4. Information in the instructions for use

(f) where applicable, information allowing the healthcare professional to verify if the device is suitable and select the corresponding software and accessories;

(ab) for devices that incorporate electronic programmable systems, including software, or software that are devices in themselves, minimum requirements concerning hardware, IT networks characteristics and IT security measures, including protection against unauthorised access, necessary to run the software as intended.

NOTE: We only list direct GSPR requirements – addressing software specifically.

Other applicable requirements (1-23) have to be fulfilled as well – they are not addressed here.

General Safety and Performance Requirements - GSPR

GENERAL REQUIREMENTS

1.Performance, safety, effectiveness

2.Reduce risks as far as possible

3.Risk management system

4.Risk control measures

5.Use error

6.Lifetime of the device

7.Transport and Storage

8.Known and foreseeable risks, side effects, benefit-risk

9. Devices listed in Annex XV

REQUIREMENTS REGARDING DESIGN AND MANUFACTURE

10. Chemical, physical and biological properties

11. Infection and microbial contamination

12. Devices incorporating a substance considered to be a medicinal product

13.Devices incorporating materials of biological origin

14.Construction of devices and interaction with their environment

15.Devices with a diagnostic or measuring function

16.Protection against radiation

17.Electronic programmable systems

18.Active devices and devices connected to them

19.Particular requirements for active implantable devices

20.Protection against mechanical and thermal risks

21.Protection against the risks posed to the patient or user by supplied energy or substances

22.Protection against the risks posed by medical devices intended by the manufacturer for use by lay persons

REQUIREMENTS REGARDING THE INFORMATION SUPPLIED WITH THE DEVICE

23.Label and instructions for use

Clinical Evaluation and Post-Market Surveillance

Regarded as tools for

- Identification of hazards
- Evaluation of risks
- Demonstration of conformity

Addressed in several Articles and in Annexes of MDR:

Clinical evaluation:

CHAPTER VI

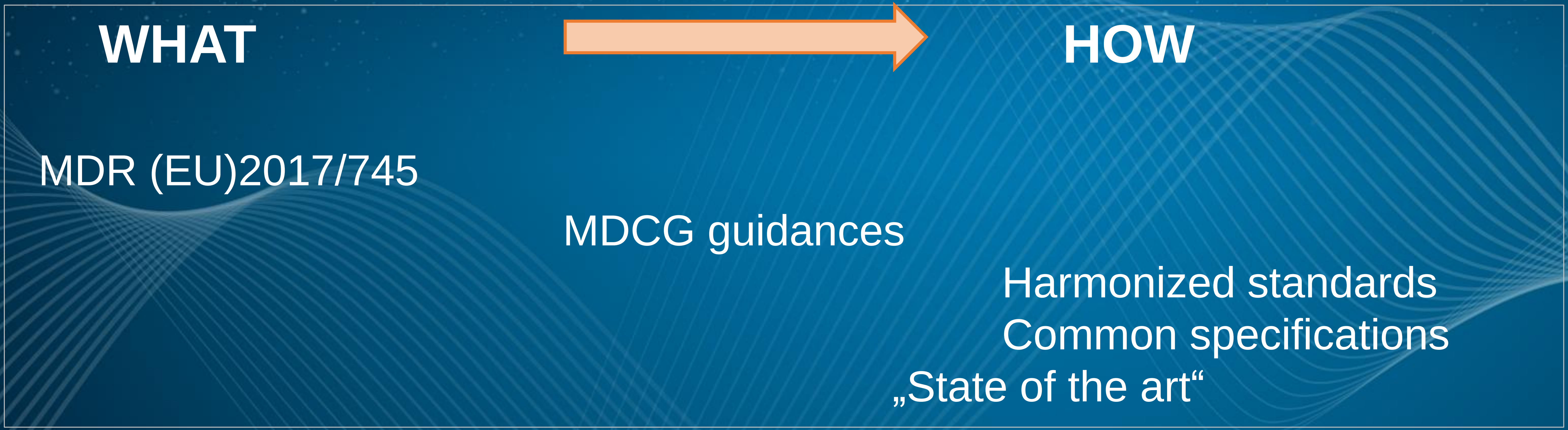
- Article 61 (Clinical evaluation)
- Articles 62-82 (Clinical investigation related)
- Annex XIV (Clinical evaluation and post-market clinical follow-up)

Post-Market Surveillance:

CHAPTER VII, SECTION 1

- Articles 83-86 (PMS, PMS plan, PMS report , PSUR – Periodic Safety Update Report)
- Annex III (Technical documentation on PMS)

Guidelines, Standards and Common specifications



WHAT

HOW

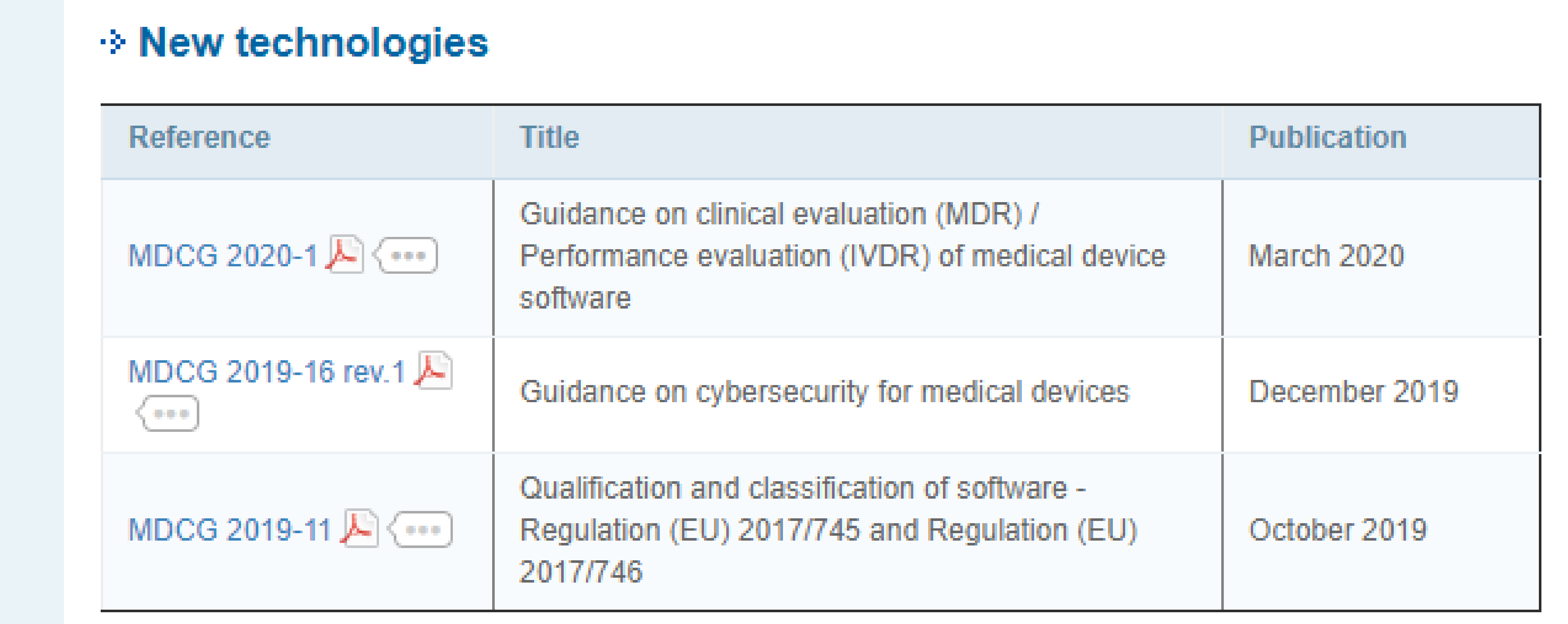
MDR (EU)2017/745

MDCG guidances

Harmonized standards
Common specifications
„State of the art“

Which guidelines? and Which standards?

Guidelines and Standards



New technologies

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

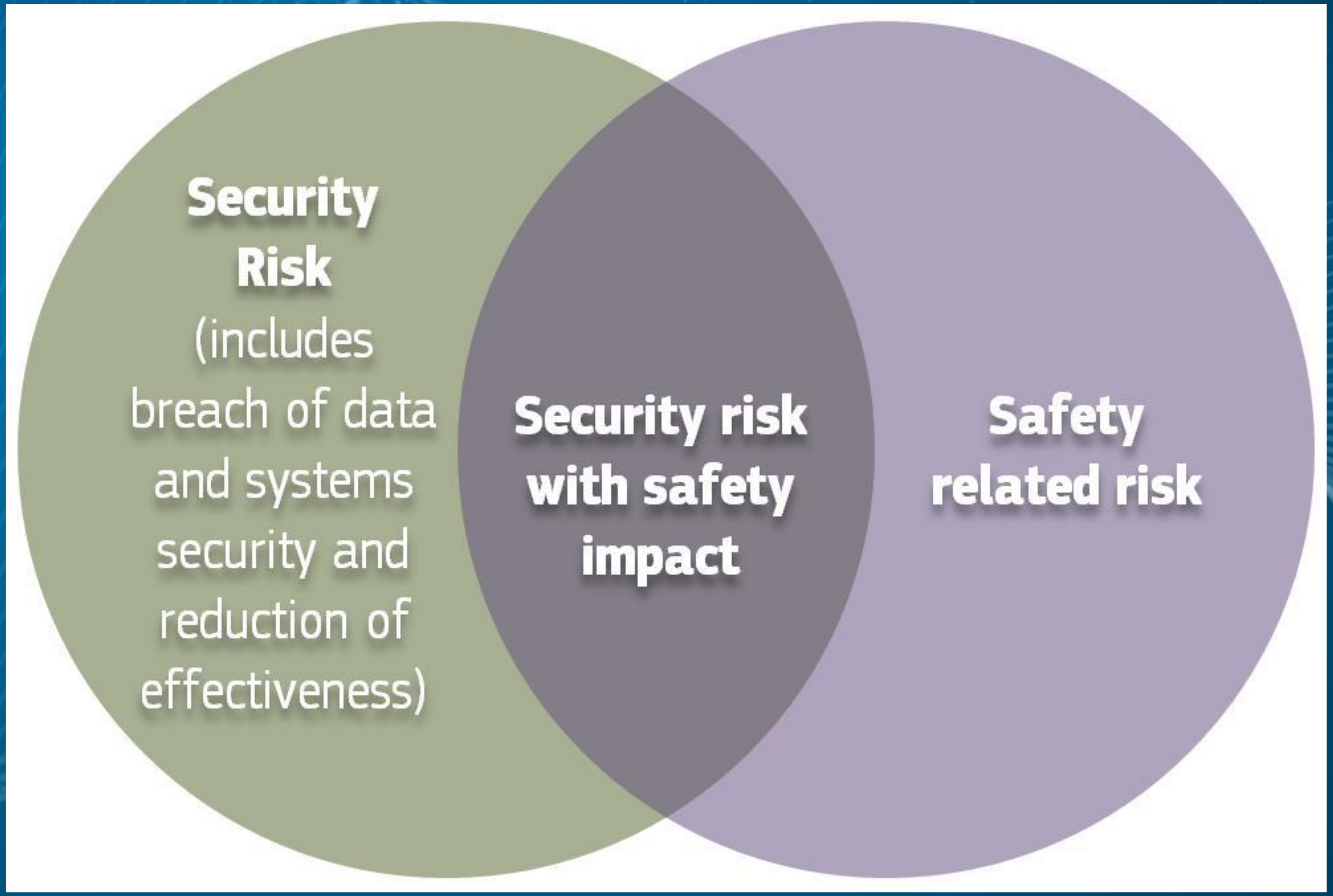
Web address:
https://ec.europa.eu/health/md_sector/new_regulations/guidance_en

MDCG 2019-16 rev.1
Guidance on Cybersecurity for medical devices

- Several paragraphs of Regulation (EU) 2017/745 (MDR) address the appropriateness of medical devices for new technological challenges, related to cyber security risks.
  New safety requirements are published (for devices with MDSW and for the SaMD)
- MDCG 2019-16 – guidance about how to comply with requirements (Annex I to MDR - GSPR) regarding the cyber security (pre-market & post-market)
- Expectations and obligations of stakeholders

Basic Cybersecurity Concepts

- IT Security, Information Security, Operation Security
- Safety, Security and Effectiveness
- Intended use and intended operational environment of use
- Reasonably foreseeable misuse
- Operating Environment
- Joint Responsibility - Specific expectations from other stakeholders (integrator, operator, users – wide range)


Security Risk (includes breach of data and systems security and reduction of effectiveness)
Security risk with safety impact
Safety related risk

Documentation and Instructions for Use

- Documentation (technical documentation)
- Instructions for Use (from the Cybersecurity perspective)
- Information to be provided to healthcare providers

Other items:

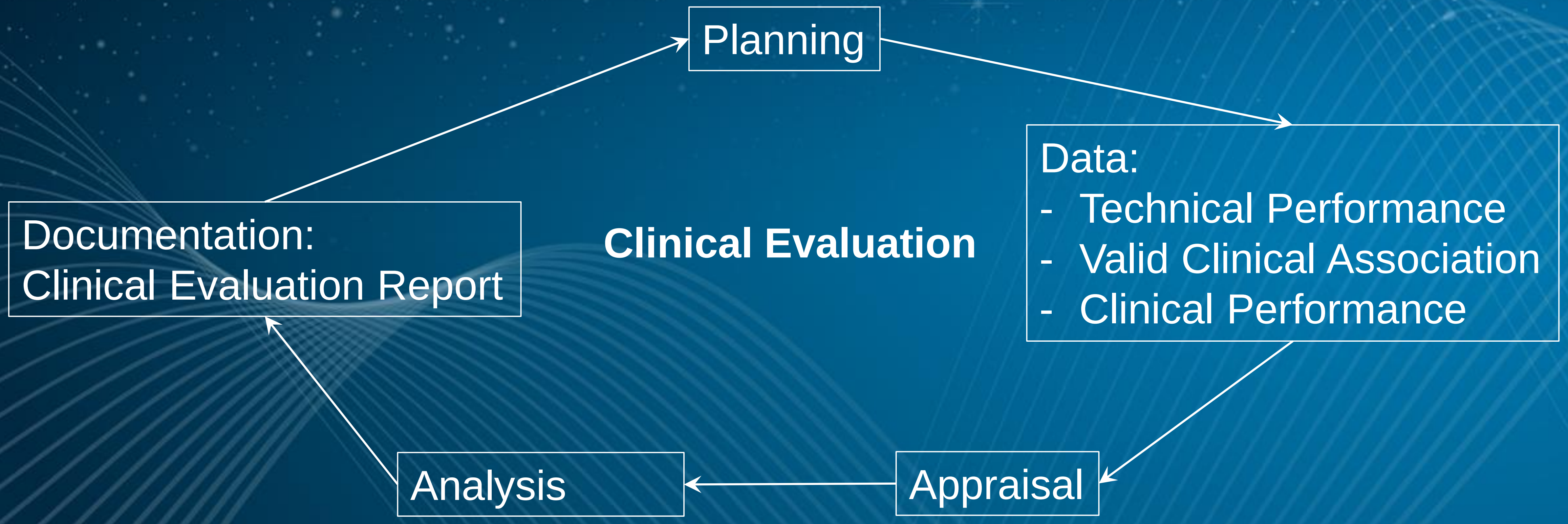
- Post-Market Surveillance (PMS) and Vigilance
- Other Legislation and guidance:
  - NIS Directive (Network and Information Security)
  - GDPR (General Data Protection Regulation)
  - EU Cybersecurity Act
  - IMDRF Guide on Cybersecurity of Medical Devices -Medical Device Cybersecurity Guide TBD

MDCG 2020-1 Guidance on Clinical/Performance Evaluation of Medical Device Software

A framework and principles for the determination of the appropriate level of CLINICAL EVIDENCE required for MDSW to fulfil the GSPR.

Each indication and claimed CLINICAL BENEFIT that is part of the INTENDED PURPOSE should be assessed individually and have the supporting CLINICAL EVIDENCE.

Clinical/Performance evaluation – an ongoing process



Planning

Data:
- Technical Performance
- Valid Clinical Association
- Clinical Performance

Appraisal

Analysis

Documentation:
Clinical Evaluation Report

Clinical Evaluation

Technical Performance: ability to accurately, reliably and precisely generate the intended output, from the input data (V&V)

Valid Clinical Association: sound connection of MDSW outputs with the targeted physiological state or clinical condition.

Clinical Perfomance: ability to yield clinically relevant output in accordance with the intended purpose.

Amount and Quality of data

Sufficient Amount

- Support the intended use, indications, target groups, clinical claims and contraindications?
- Have clinical risks and clinical performance been investigated?
- Have relevant MDSW’s characteristics been considered?
- How big is the body of scientific evidence?

Sufficient Quality

- Appropriateness to meet the research objectives
- State of the art of data
- Appropriateness of statistical approach
- ethical, legal and regulatory considerations
- Possible conflict of interests

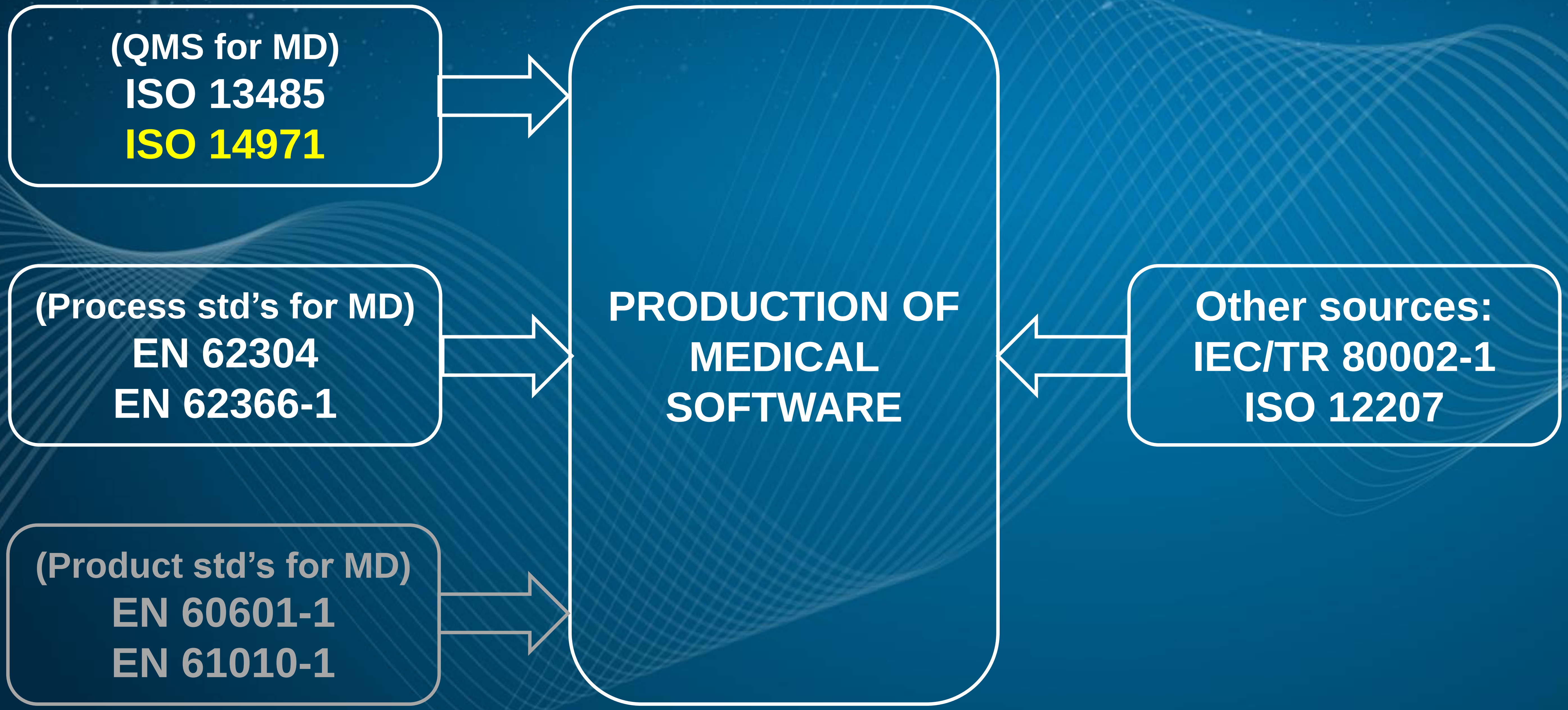
*CLINICAL EVALUATION of class III and implantable devices (MDR), shall include data from a CLINICAL INVESTIGATION unless the conditions of Article 61(4), (5) or (6) of the MDR have been fulfilled.

Standards … some of them*

- ISO 13485 Medical devices - Quality management systems - Requirements for regulatory purposes
- **IEC 62304 Medical device software - Software life-cycle processes**
- IEC 82304-1 Health software – Part 1: General requirements for product safety
- **ISO 14971 Medical devices - Application of risk management to medical devices**
- **IEC/TR 80002-1 Guidance on the application of ISO 14971 to medical device software**
- ISO/IEC 27000 Information security Management Systems
- **IEC 62366 Medical devices - Application of usability engineering to medical devices**
- ISO 15223-1 Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements
- IEC 60601-x-x Medical electrical equipment - General requirements for basic safety and essential performance (a family of standards – collateral & particular standards)

*for the sake of clarity, standards are not referenced to completely (edition, year of publication, EN edition)

Groups of standards



(QMS for MD)
ISO 13485
ISO 14971

(Process std's for MD)
EN 62304
EN 62366-1

(Product std's for MD)
EN 60601-1
EN 61010-1

PRODUCTION OF MEDICAL SOFTWARE

Other sources:
IEC/TR 80002-1
ISO 12207

EN ISO 14971:2019 (Risk management)

- Risk management process definition
- Generic standard for medical devices / MDSW specifics are neglected
- Use of **IEC/TR 80002-1** is advised
  - Application to MDSW
  - Annexes B and C (Examples and pitfalls)
- Inputs:
  - Clinical evaluation results
  - Post-market surveillance results
  - Usability study results (use of EN 62366-1:2015 is advised)

EN 62304:2006 (SDLC)

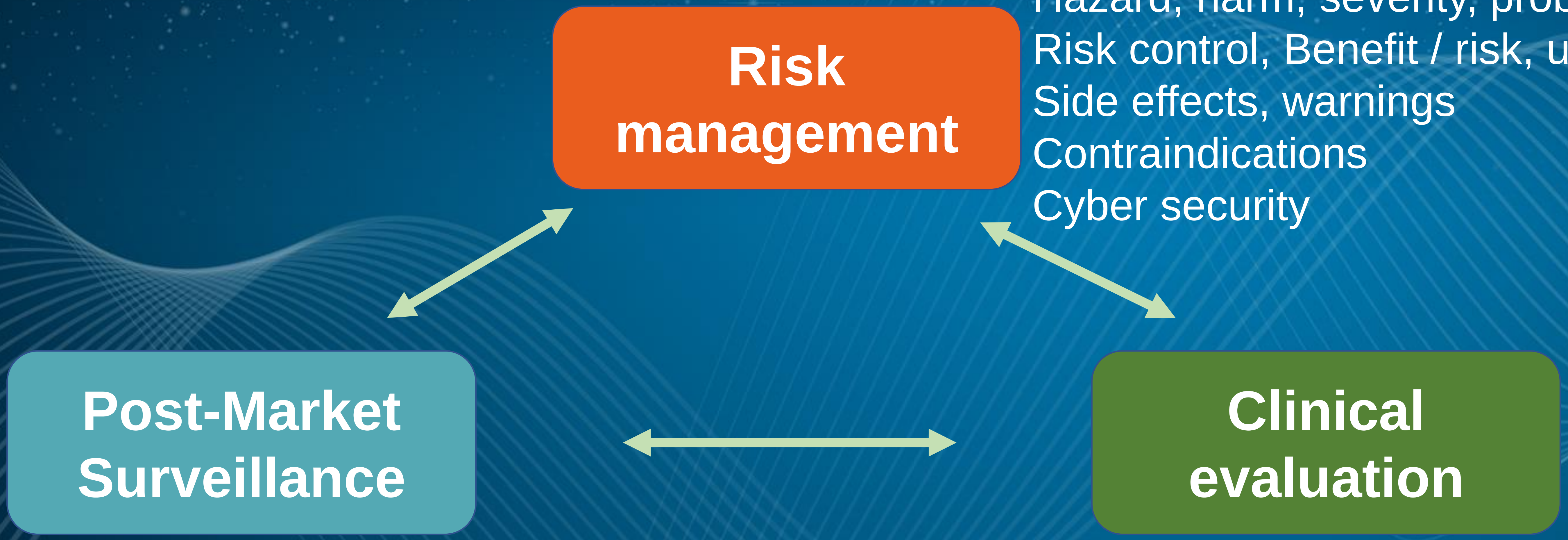
Purpose: process!

- Main requirement: creation and establishment of processes for development and maintenance of MDSW.
  Emphasis: reduction of risks for patients and other stakeholders
  (see EN ISO 14971)

Processes addressed:

- Development
- System Maintenance
- Risk management
- SW configuration management
- SW problem resolution

Interdependency of the three fields



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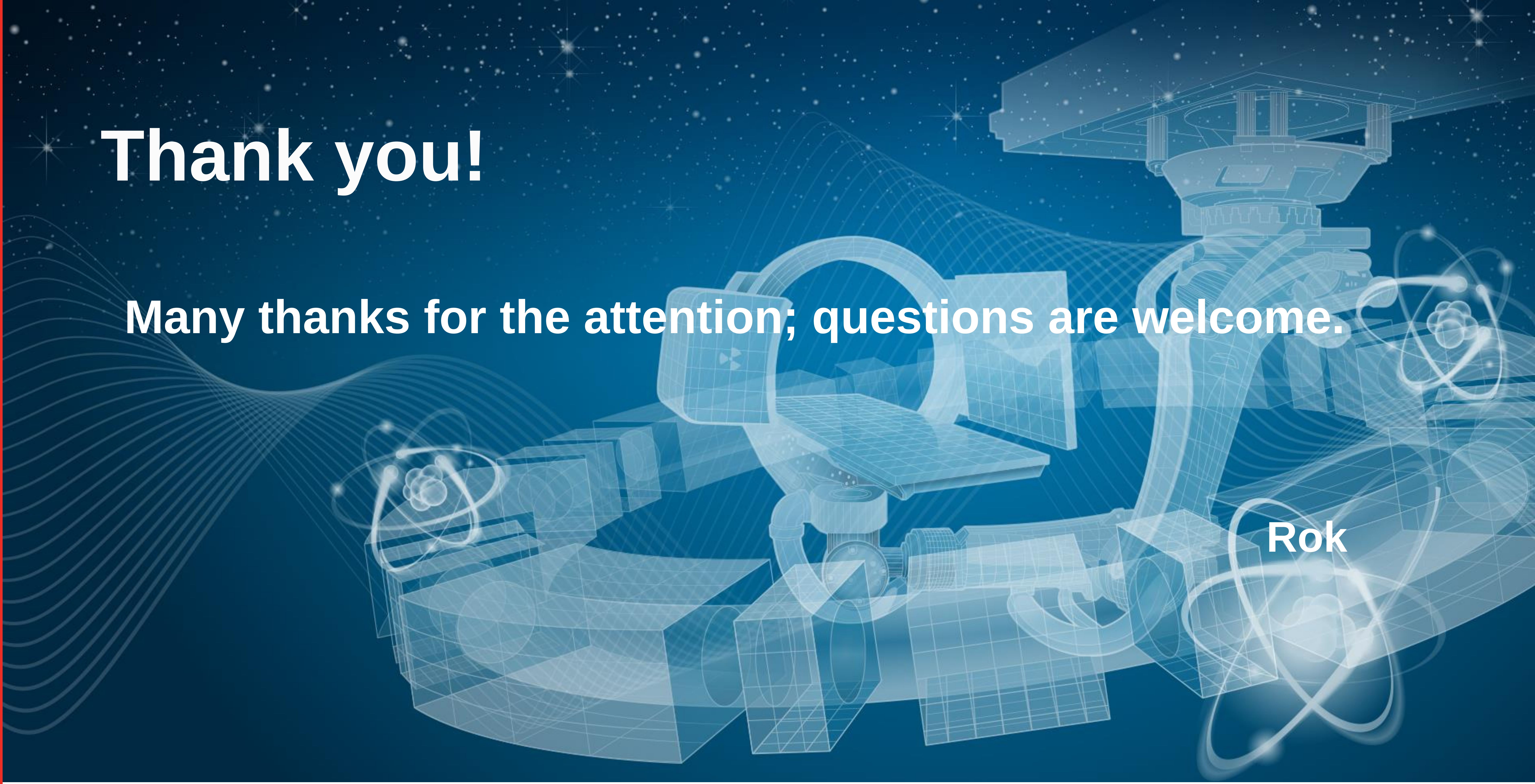
Clinical performance
Scientific validity



Thank you!

Many thanks for the attention; questions are welcome.

Rok