



Artificial Intelligence in cancer drug development – Regulatory considerations

Katrin Rupalla & Cheng Zhang
Johnson & Johnson Innovative Medicines



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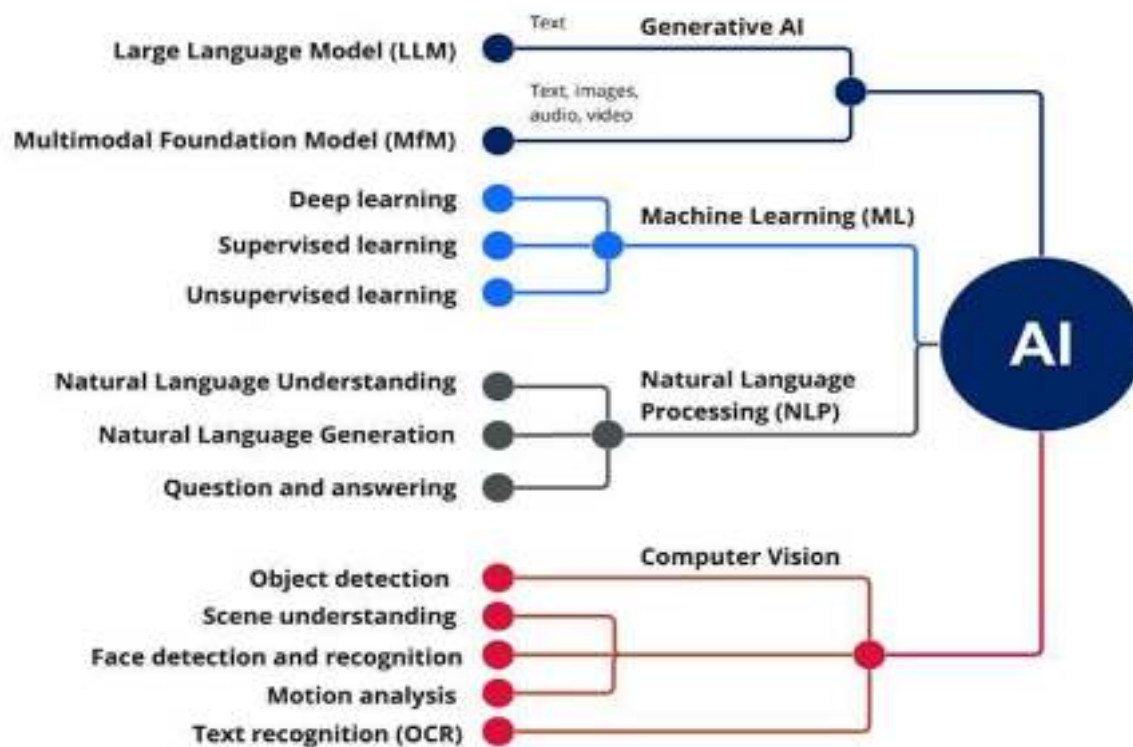
Domains of artificial intelligence (AI)*

Gen AI creates new content such as text, images, voice, video etc. by learning from data pattern, e.g. ChatGPT

ML allows computers to autonomously learn and improve without being explicitly programmed. ML algorithms are trained on data to make predictions or decisions.

NLP deals with the ability of computer systems to understand and generate human language. NLP algorithms are used to analyse text, comprehend, converse with users and perform tasks like translation, question answering.

CV empowers computers to 'see' and comprehend the visual world, analysing images and videos like humans and analyse these for object detection, face recognition etc.



*<https://www.digital.nsw.gov.au/policy/artificial-intelligence/a-common-understanding-simplified-ai-definitions-from-leading>



AI across health-care delivery and drug development

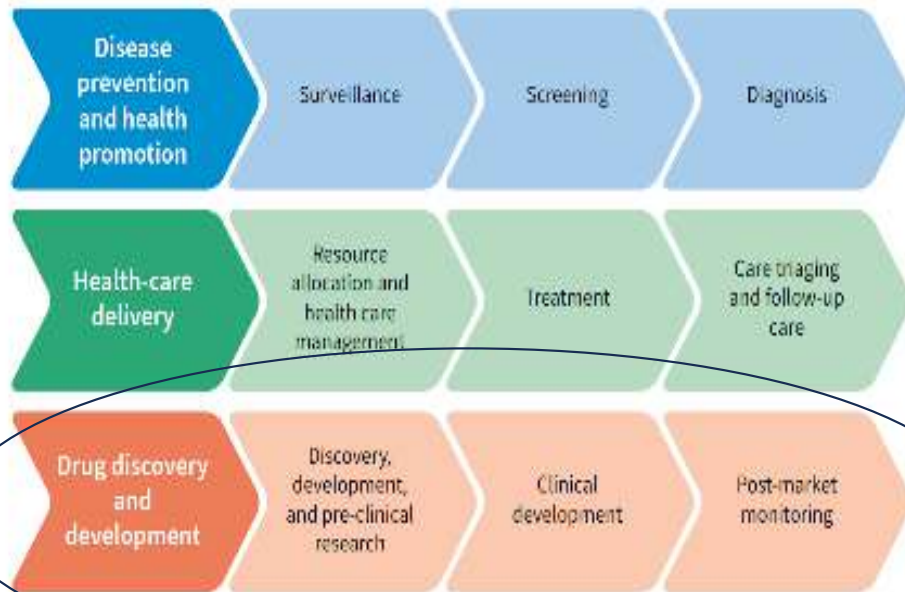


FIGURE 1. A general spectrum of AI research and development in health-care delivery and therapeutic development





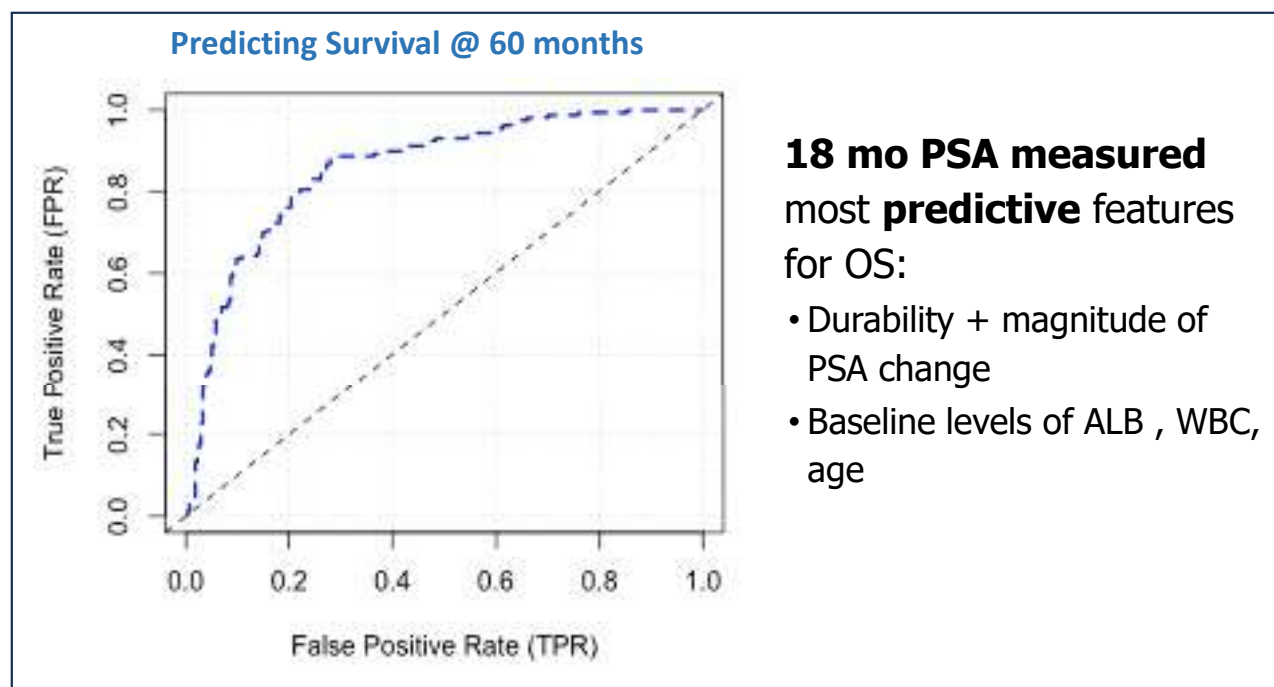
Examples of AI use cases in cancer drug development



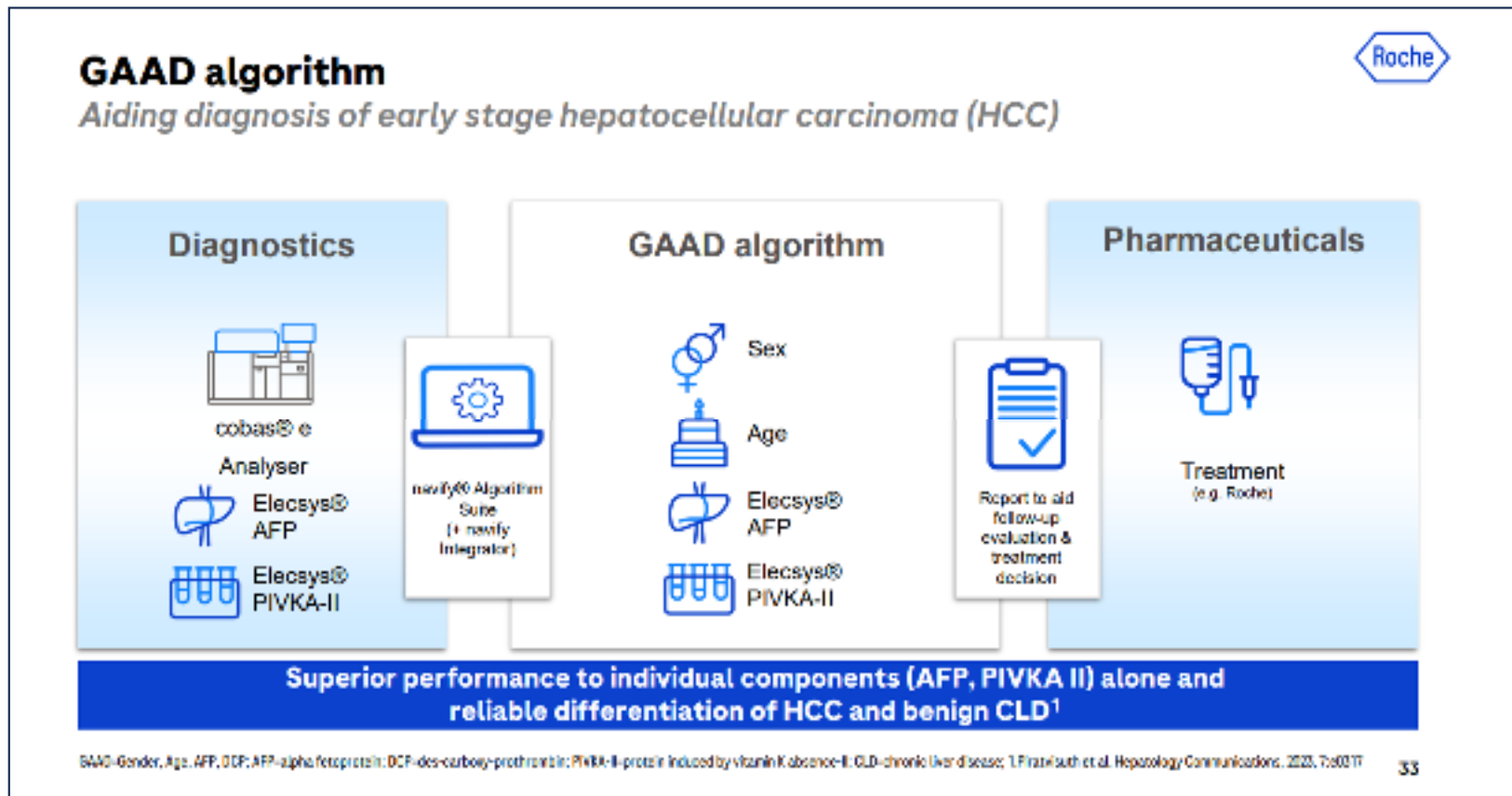
AI predicts durable outcomes in metastatic prostate cancer based on PSA

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- **Background:** Can **early endpoints** using PSA measurements **reduce the readout time** of trials for pts with metastatic prostate cancer
- **Data:** Clinical and PSA data were obtained from **6 randomized, double-blind, phase 3 trials** (6,451 pts, >85K PSA values)
- **Result:** Lead **model can predict OS at 60 months** using <4 months of PSA data (AUC ~ 0.8).
- **Next steps:** Apply to therapies in early development to evaluate potential for durable benefit



AI applied to clinical data to aid diagnosis of early-stage HCC*





AI applied to reduce interpretation time in real-world clinical setting*

Scientific evidence: Automated Chest CT Assistance Impact on Interpretation Times in a Real-World Clinical Setting





22.1% reduction in Chest CT interpretations times

Scientific article:
The objective was to evaluate the impact of an automated AI platform, that is integrated into clinical workflow for Chest CT interpretation, on radiologists' interpretation times when evaluated in a real-world clinical setting, in a prospective randomized study.

Pocock et al.¹, Medical University of South Carolina, USA

Improve Clinical Efficiency:
A reduction in Chest CT interpretation times in the real-world clinical setting



22.1%
Interpretation time



FDA Clears Modules of AI-Rad Companion Chest CT From Siemens Healthineers

Artificial intelligence-based software enables automated enhanced visualization of CT images of the lungs, heart and aorta

The results by Siemens Healthineers' customers described herein are based on results that were achieved in the customer's unique setting. Since there is no "typical" hospital and many variables exist (e.g. hospital size, case mix, level of IT adoption) there can be no guarantee that other customers will achieve the same results.
1 Pocock et al. (2021). Impact of Artificial Intelligence assistance on Chest CT interpretation Times: A prospective randomized study.

* Unrestricted © Siemens Healthineers, 2024



Public private partnerships: IDERHA project of federated AI development in lung cancer



Leveraging existing Lung Cancer data & AI models

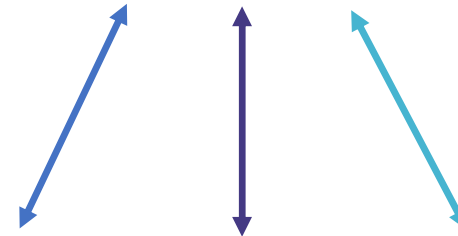
Central AI Manager
University of Luxembourg



AI Algorithm & Models
Frauenhofer Institute Bonn &
Technical University Munich

AI personalized
malignancy risk prediction
CT-Scan (DICOM)

AI personalized early risk
profiling
EHR (OMOP)



**Local Data Holders Data
Access NOT Sharing**



Large Hospitals
Regions / Country





Regulatory considerations of using AI in drug development



Key EU regulatory documents

European Parliament
2019-2024



TEXTS ADOPTED

P9_TA(2024)0138

Artificial Intelligence Act

European Parliament legislative resolution of 13 March 2024 on the proposal for a regulation of the European Parliament and of the Council on laying down harmonised rules on Artificial Intelligence (Artificial Intelligence Act) and amending certain Union legislative Acts (COM(2021)0206 – C9-0146/2021 – 2021-0106/COD)

(Ordinary legislative procedure: first reading)

General interpretation by EFPIA, AI systems and models specifically developed & put into service for **sole purpose of scientific research & development are excluded from its scope** (Recital 25, Articles 2.6 and 2.8)

https://www.europarl.europa.eu/doceo/document/TA-9-2024-0138_EN.pdf



14 November 2023
EMA/CMP/C4MT/5003/2023
Consultation on Medical Products for Veterinary Use (CMPV)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Regulatory considerations on use of AI and ML in lifecycle of medicinal product.
Focus on **scientific principles for regulatory evaluation** when applied to support **safe and effective development and use of medicines**.

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf



Workplan focusing on four critical dimensions to facilitate the development and use of responsible and beneficial AI: 1) Guidance, policy and product support; 2) Tools & technologies; 3) Collaboration and change management; and 4) Experimentation.

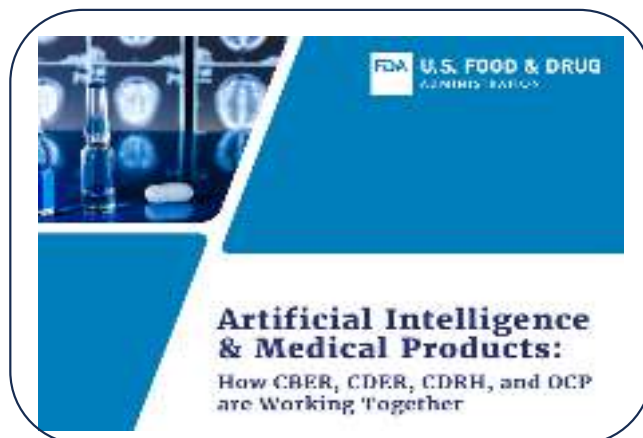
https://www.ema.europa.eu/en/documents/work-programme/multi-annual-artificial-intelligence-workplan-2023-2028-hma-ema-joint-big-data-steering-group_en.pdf



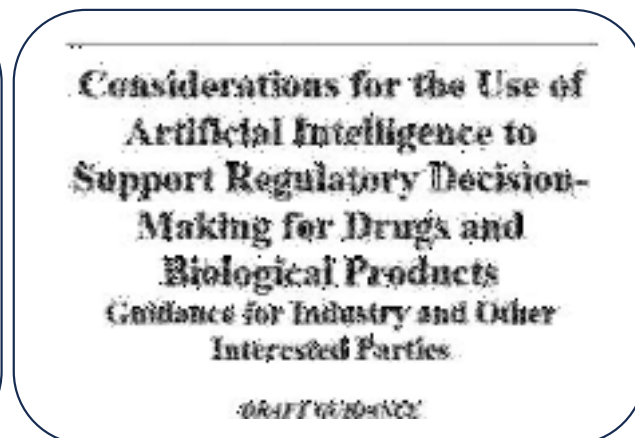
Key FDA regulatory documents



Discussion paper to facilitate the **use of AI&ML in drug development**, including in the development of **medical devices intended to be used with drugs**, to help inform the regulatory landscape in this area.



Discussion paper provide greater transparency regarding how **FDA's medical product Centers are collaborating**. AI management requires a **risk-based regulatory framework** built on robust principles, standards, best practices, and state-of-the-art regulatory science tools.



To be published

Guidance based on FDA's experience with reviewing over 300 submissions with AI

<https://www.fda.gov/media/167973/download>



EU regulatory considerations when using AI in drug development

1. European Medicines Agency (EMA): Drug perspective
2. Notified Body (NB): Device & diagnostic perspective
3. Member States: Clinical trial authorization



EMA regulatory perspective from the product side

Low risk	Medium risk	High risk
- Models used more <u>descriptively</u> and complementing available data, e.g.: - Description of population PK characteristics	- Models used to <u>provide additional evidence</u>, e.g.: - Dose selection - Study design	- Models used to <u>make decisions</u>, e.g.: - Predict new dosing regimen - Treatment decisions, patient enrichment - Endpoint in clinical trial

Regulatory requirements increasing





EMA assesses AI with high impact on drug regulatory decision making

- Key areas of scrutiny based on level of risk:
 - Data acquisition and augmentation
 - Training, validation, and test data
 - Model development
 - Performance assessment
 - Interpretability and explainability
 - Governance, data protection
 - Integrity aspects, ethical and trustworthy aspects
- Interaction with EMA, e.g. via Qualification, scientific advice process, Innovation Task Force





NB: Assess AI device or in vitro diagnostic & CE mark

Medical Device Regulation (**MDR**)

5.5.2017 EN Official Journal of the European Union L 117

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

In vitro Diagnostic Medical Devices Regulation (**IVDR**)

L 117/176 EN Official Journal of the European Union 5.5.2017

REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

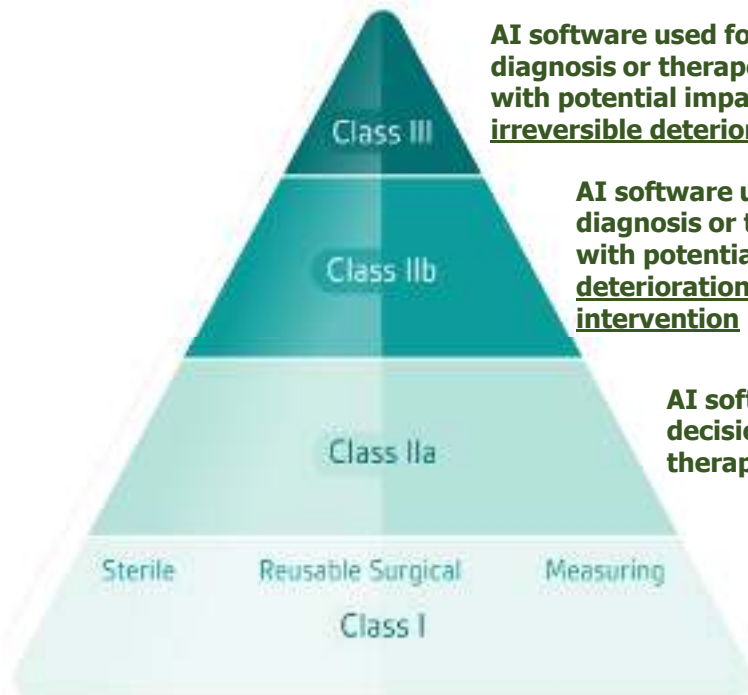
on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)



Step 1: Risk classification by MDR & IVDR

MDR



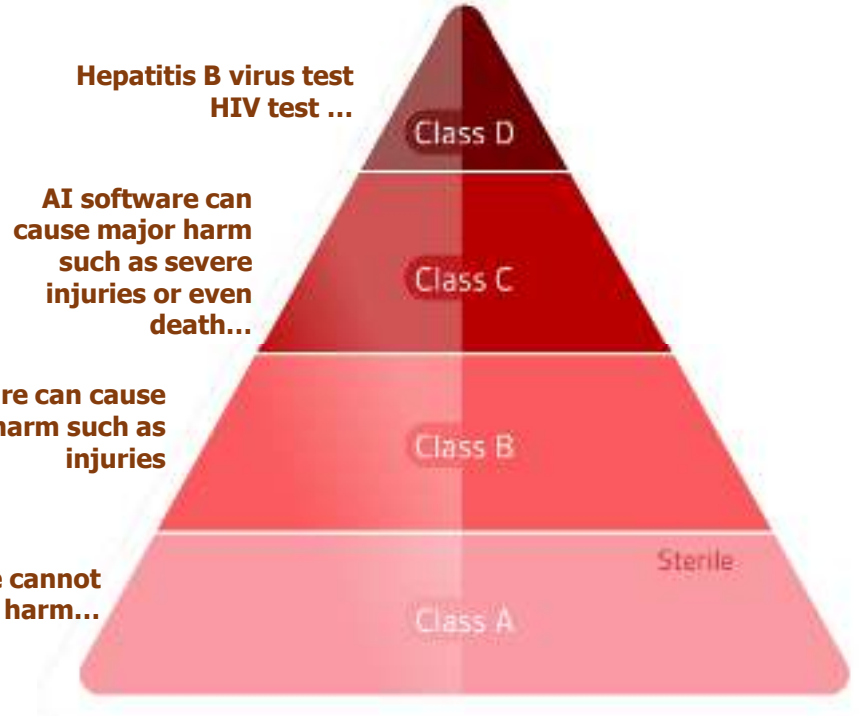
AI software used for decisions on diagnosis or therapeutic purposes with potential impact on death or an irreversible deterioration of person

AI software used for decisions on diagnosis or therapeutic purposes with potential impact on serious deterioration of a person or a surgical intervention

AI software used for decisions on diagnosis or therapeutic purposes

AI software in general

IVDR



Hepatitis B virus test
HIV test ...

AI software can cause major harm such as severe injuries or even death...

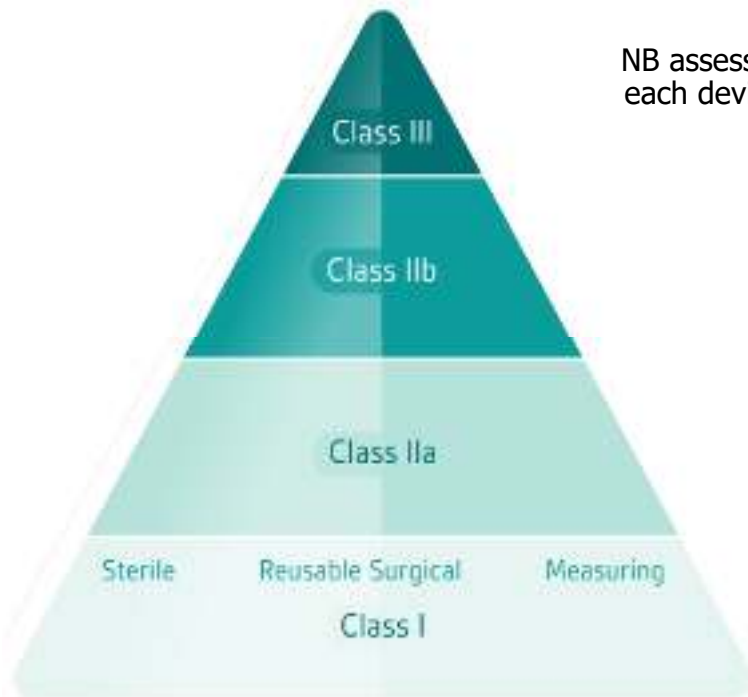
AI software can cause minor harm such as injuries

AI software cannot cause any harm...



Step 2: Risk classification determines level of scrutiny and NB involvement

MDR

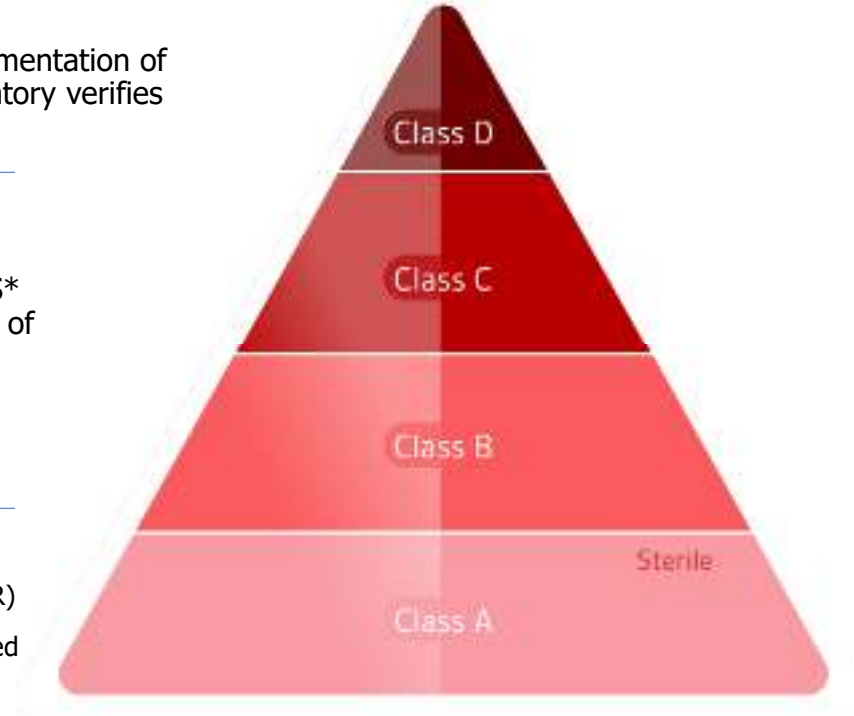


NB assesses QMS* and technical documentation of each device (MDR) or reference laboratory verifies batch (IVDR)

Notified Body assesses QMS* and technical documentation of minimum one device per generic device group

NB assesses QMS* related to sterility (IVDR) & others (MDR)
Self certification; no NB involved

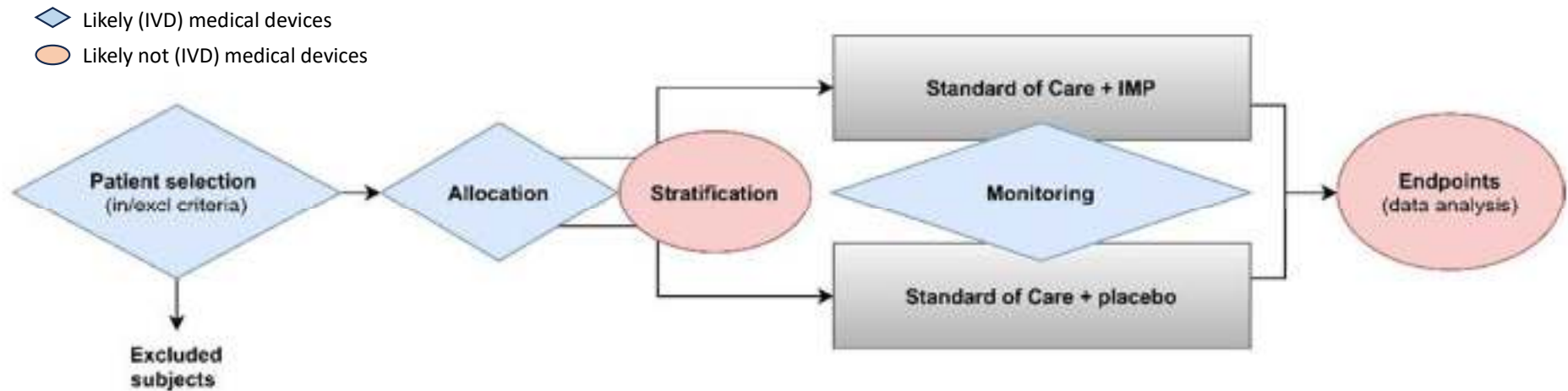
IVDR





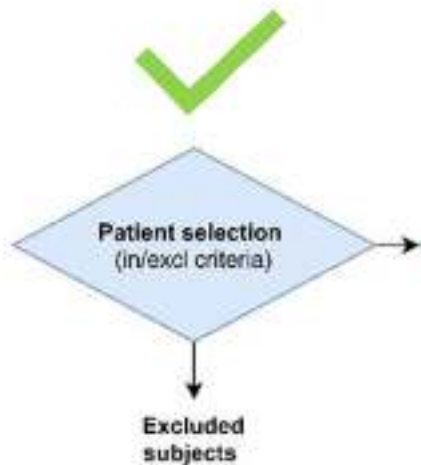
Step 3: AI used in drug clinical trial classified as medical device?

What is the “Intended Purpose” and impact on medical management?





If AI is a device in a clinical trial, what do I need to do?



Example: AI algorithm for patient selection (Class C - IVD)

1. If already CE marked for same intended use in the drug clinical trial – no device regulatory submission necessary
2. If not CE marked **or** intended use in the trial different from CE mark – need application or notification to Member States where the trial is conducted
3. Special scenario: If qualified as an “In-house device” – no device regulatory submission necessary



FDA: Regulatory considerations

- FDA focuses on three key areas of AI/ML in the context of drug development:
 - Human-led governance, accountability, and transparency
 - Quality, reliability, and representativeness of data
 - Model development, performance, monitoring, and validation
- Pathways to engage with FDA
 - IND meetings
 - Drug Development Tool (DDT) Qualification Programs
 - Innovative Science and Technology Approaches for New Drugs (ISTAND) Program
 - Other: NOTE, CPIM, MIDD, RDEA ...



FDA's ISTAND Pilot Program accepts submission of first artificial intelligence-based and digital health technology for neuroscience

1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12

11/02/2024 FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) today accepted the first submission into the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program. The submission is for a first-in-class, artificial intelligence-based digital health technology that will be used to predict and monitor adverse events in patients with COVID-19.

The submission is for a first-in-class, artificial intelligence-based digital health technology that will be used to predict and monitor adverse events in patients with COVID-19. The technology is a machine learning model that can identify potential adverse events in patients with COVID-19. The model is trained on a large dataset of patient data and can identify potential adverse events in patients with COVID-19. The model is trained on a large dataset of patient data and can identify potential adverse events in patients with COVID-19.



Conclusions

- Multitude of possibilities to use AI in drug development
- Data availability/quality/access key to be able to build tools
- Several EU regulatory documents published
- If used regulatory considerations include:
 - Impact on regulatory decision making, risk and intended use determine level of regulatory scrutiny
 - EU more complex from device/IVDR perspective – WATCH OUT during clinical trial application process



Regulatory complexity for CE marking of AI software

- Three separate regulatory frameworks with different risk classification:
 - EU Artificial Intelligence Act (AIA)
 - Medical Device Regulation (MDR)
 - In vitro Diagnostic Medical Devices Regulation (IVDR)



Original slide from S. Seifert, DG Connect AI Policy Dev & Coordination

