[WEBINAR] REGULATING AI-BASED MEDICAL DEVICES

Thursday, 25th June 2020 | 9am to 10:30am (GMT +8)

APACMed
The voice of MedTech

SPEAKERS:

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MODERATOR:

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Thursday, 25th June 2020
09am to 10.30am (Singapore time)

Organised by: APACMed

Technical instructions

If you have any questions you'd like to ask, please share them with us via the chat function;

we will respond to them at the end of the presentation.

APACMed Digital Health Committee

30+ COMPANIES:
MNCs
SMEs
Start-ups

2 OBJECTIVES:
- ❑ **Create and Share knowledge**
- ❑ **Advocate for regional policies**

AREAS OF WORK:

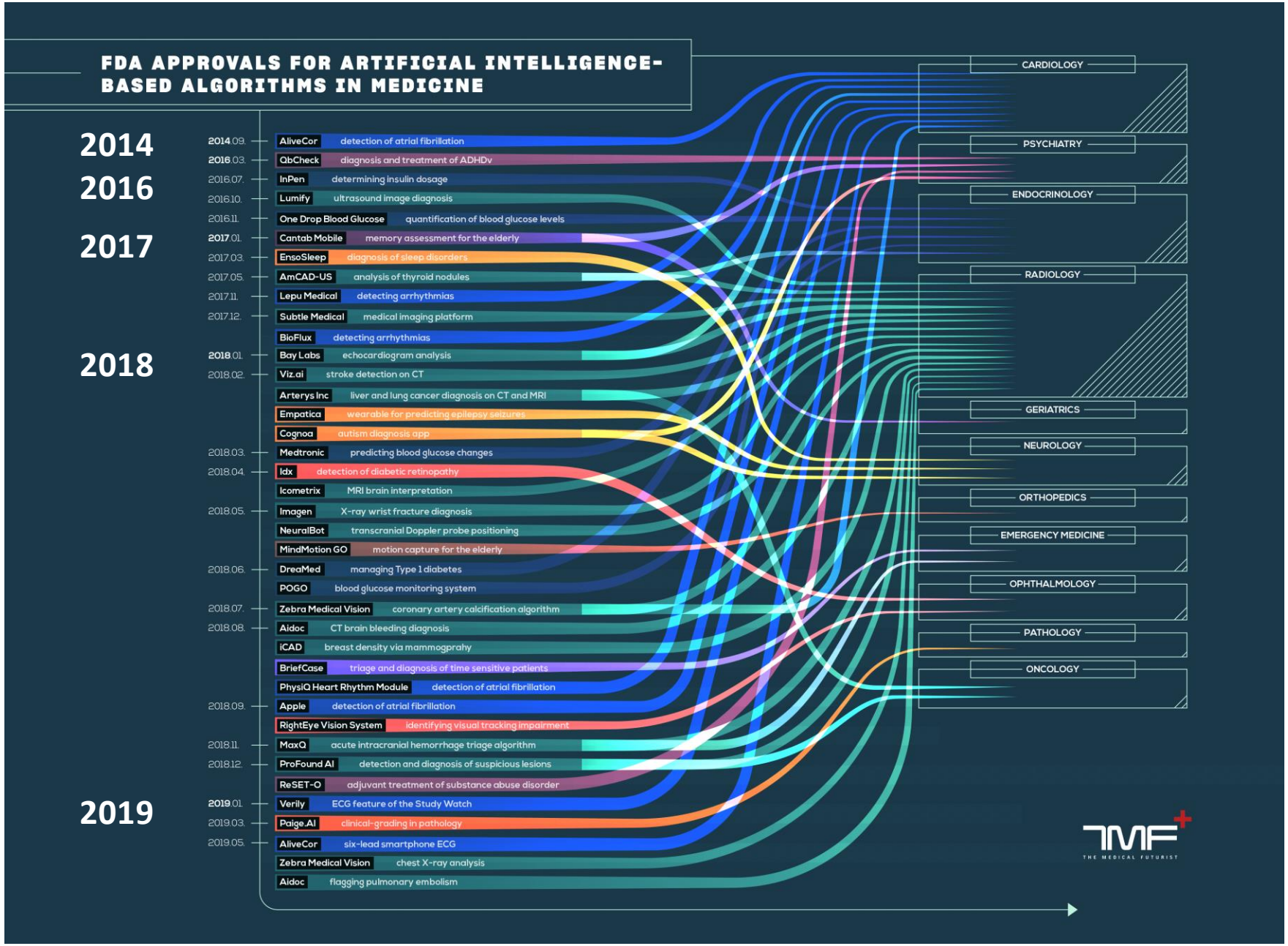
Cybersecurity | Interoperability | Reimbursement | Regulatory | Transversal

Evolutions in the Regulation of Artificial Intelligence

Artificial Intelligence(AI) in Healthcare: Policies and Regulations in Asia-Pacific

Nathan A. Carrington, Ph.D., Senior Regulatory Policy Advisor

Roche Diagnostics



https://medicalfuturist.com/fda-approvals-for-algorithms-in-medicine

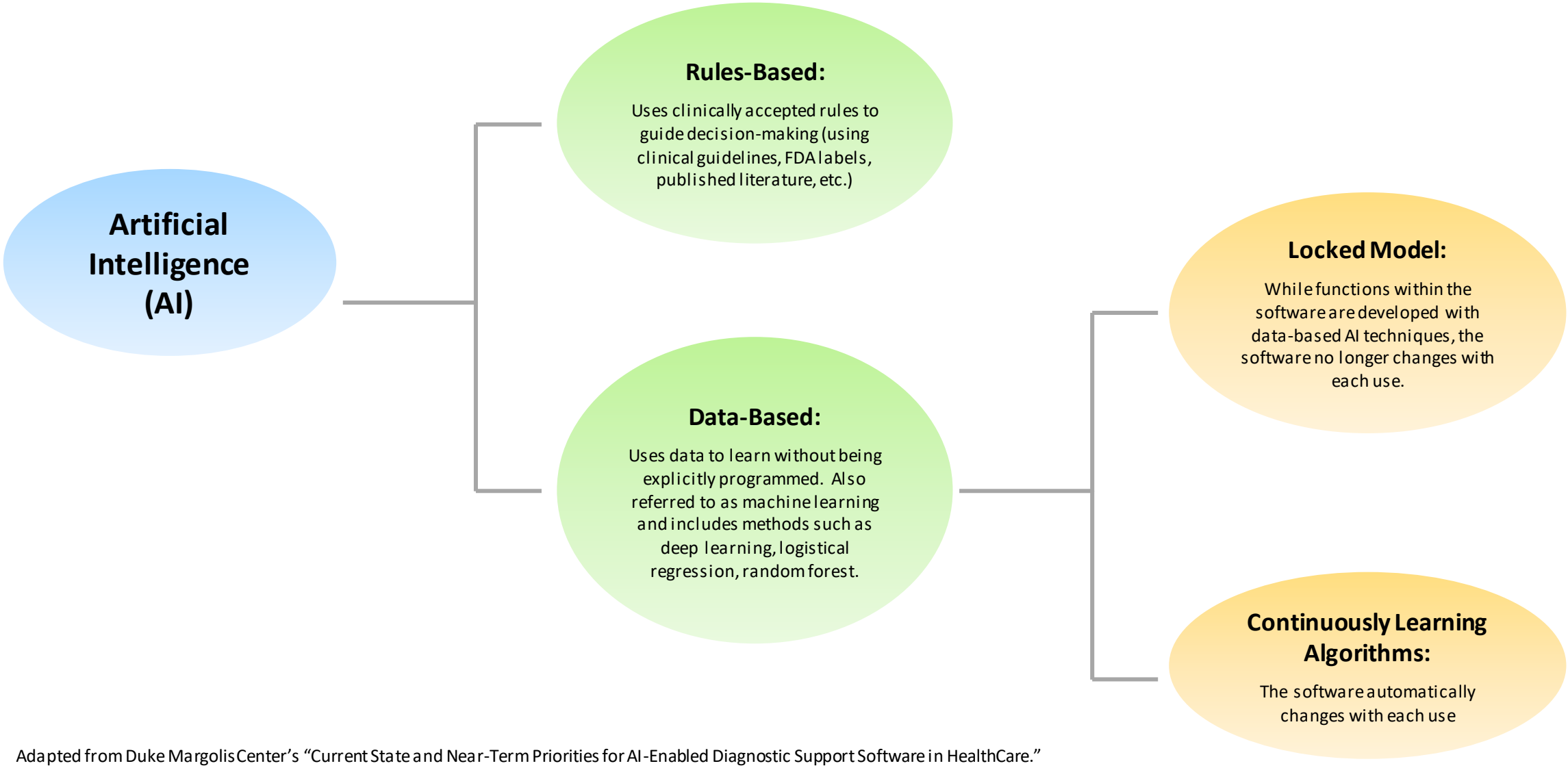
US FDA Clearances/Approvals spanning multiple disciplines including:

- Cardiology
- Psychiatry
- Endocrinology
- Radiology
- Geriatrics
- Neurology
- Orthopedics
- Emergency Medicine
- Ophthalmology
- Pathology
- Oncology

The development and commercialization of **AI-Based algorithms** that qualify as **medical devices** is **accelerating** at a rapid rate.

Types of AI

Rules-Based vs. Data-Based, Locked vs. Continuous Learning



Adapted from Duke Margolis Center's "Current State and Near-Term Priorities for AI-Enabled Diagnostic Support Software in HealthCare."
https://healthpolicy.duke.edu/sites/default/files/atoms/files/dukemargolisaienableddxss.pdf

Types of AI-Based Software

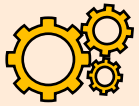
Regulatory Implications

Rules-Based

- Conceptually straightforward, can be represented by a flow diagram.
- Generally lower-risk functions due to their high degree of transparency and interpretability.

Data-Based: Locked Models

- Employed by most currently marketed AI-based SaMD.
- Updated periodically – modifications must undergo regulatory review depending on the significance of the change.
- Performance may degrade over time if not updated.



Data-Based: Continuous Learning Models

- Automatically changes over time, with potential impact to device safety and effectiveness.
- Unique regulatory challenges, risks, and benefits as compared to Locked Models.

SiMD vs. SaMD

AI-Based Algorithms May Be SiMD or SaMD

Software in a Medical Device (SiMD): Necessary for a hardware medical device to achieve its intended purpose. Clinical evaluation and review of the software occurs concurrently with the device itself.

Also referred to as "dependent" or "embedded" software.

Software as a Medical Device (SaMD): Intended to be used for one or more medical purposes and performs that purpose without being part of a hardware medical device, meaning the software has its own intended use.

Also referred to as "independent" or "standalone" software.

Source: *Software as a Medical Device: (SaMD): Key Definitions,* IMDRF/SaMD WG/N10FINAL:2013

Four Key Regulatory Areas of Focus for SaMD

Applicable to AI-Based Algorithms

Qualification

Classification

Clinical Evaluation

Alternative Pathways

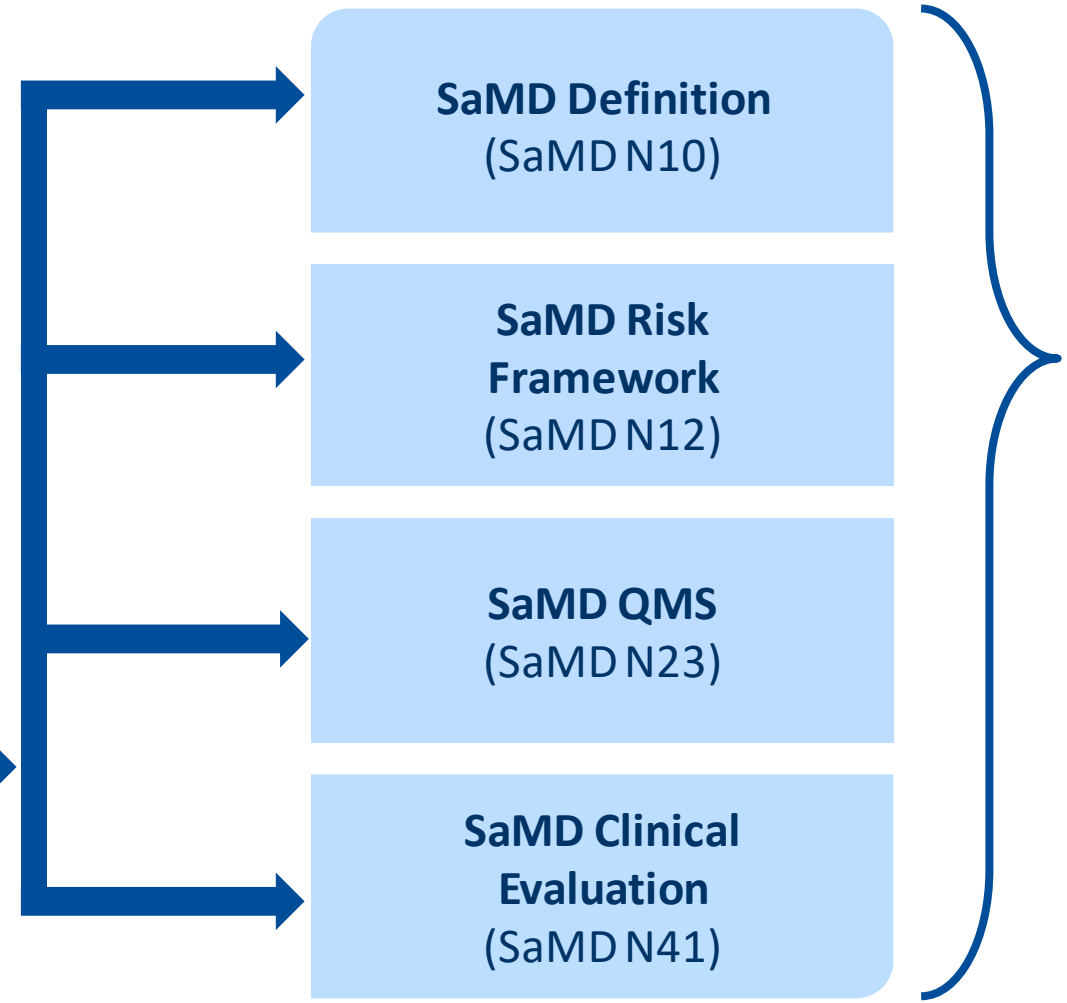
Existing SaMD-focused regulatory frameworks should be leveraged, and adapted, for the regulation of AI-based digital health products.

International Medical Device Regulators Forum (IMDRF)

Global Convergence of SaMD Regulation

Background: Medical device regulators from around the world striving toward global harmonization of regulatory requirements.

SaMD Working Group Goal: A converged, risk-based SaMD framework and associated controls.



Implementation: Implemented independently by Regulatory Jurisdictions using converged IMDRF principles

Software Qualification

Is this software regulated?

- IMDRF recognizes that only “a subset of software used in healthcare meets the definition of a medical device…”[1]
- As with all medical products, software is qualified or regulated based on whether or not it has a **medical purpose**.
  - IMDRF defines medical purpose as “software that meets the definitions of a medical device or IVD.”

Appropriate qualification of software allows regulators to focus their resources on software that presents the highest risk to patients.

[1] *Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations, IMDRF/SaMD WG/N12FINAL:2014*

Software Classification

IMDRF Risk Categorization Framework

State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

Source: *Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations,* IMDRF/SaMD WG/N12FINAL:2014

SaMD Clinical Evaluation

Utilizing IMDRF N41 Guidance

The level of evaluation and independent review should be **commensurate with the risk** posed by the specific SaMD

Clinical Evaluation		
Valid Clinical Association	**Analytical Validation**	**Clinical Validation**
Is there a valid clinical association between your SaMD output and your SaMD's targeted clinical condition?	Does your SaMD correctly process input data to generate accurate, reliable, and precise output data?	Does use of your SaMD's accurate, reliable, and precise output data achieve your intended purpose in your target population in the context of clinical care?

Source: *Software as a Medical Device (SaMD): Clinical Evaluation,* IMDRF/SaMD WG/N41FINAL:2017

Additional Factors for AI-Based SaMD

Considerations in Development, Validation, and Lifecycle Management

Quality of Data Inputs

- Variety and relevance of data to the intended use
- Segregation of training and validation data sets
- Data acquired in a consistent and reliable manner

Transparency / Interpretability

- Extent to which a system is understandable by humans
- Balance between performance and trustworthiness

Usability

- Performance of the software in the hands of its intended users
- Level of reliance on the software
- Leverage IEC 62366

Risk Management

- Utilization of existing standards, such as ISO 14971 and IEC 62304
- Continuous learning vs. locked, predictability, interpretability
- AI may introduce new hazards while reducing frequency or severity of others

Real-World Performance

- Signal collection for continued development and iteration
- Leveraged for safety improvements and claims expansion

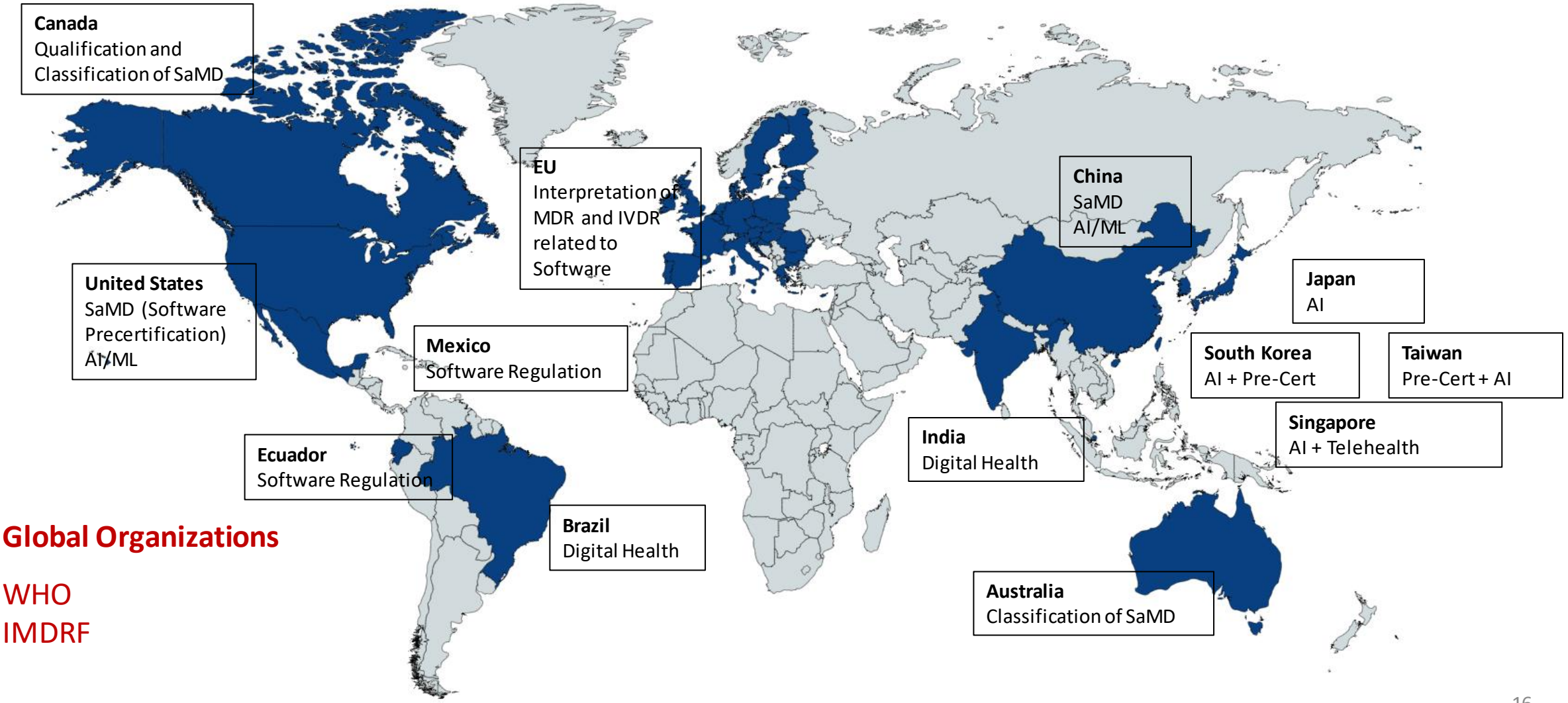
Modifications

- Changes to data inputs
- Changes to analytical and clinical performance
- Changes to intended use

Current AI Regulatory Landscape

Growing Global Interest in Software Regulation

Driving Toward Global Convergence

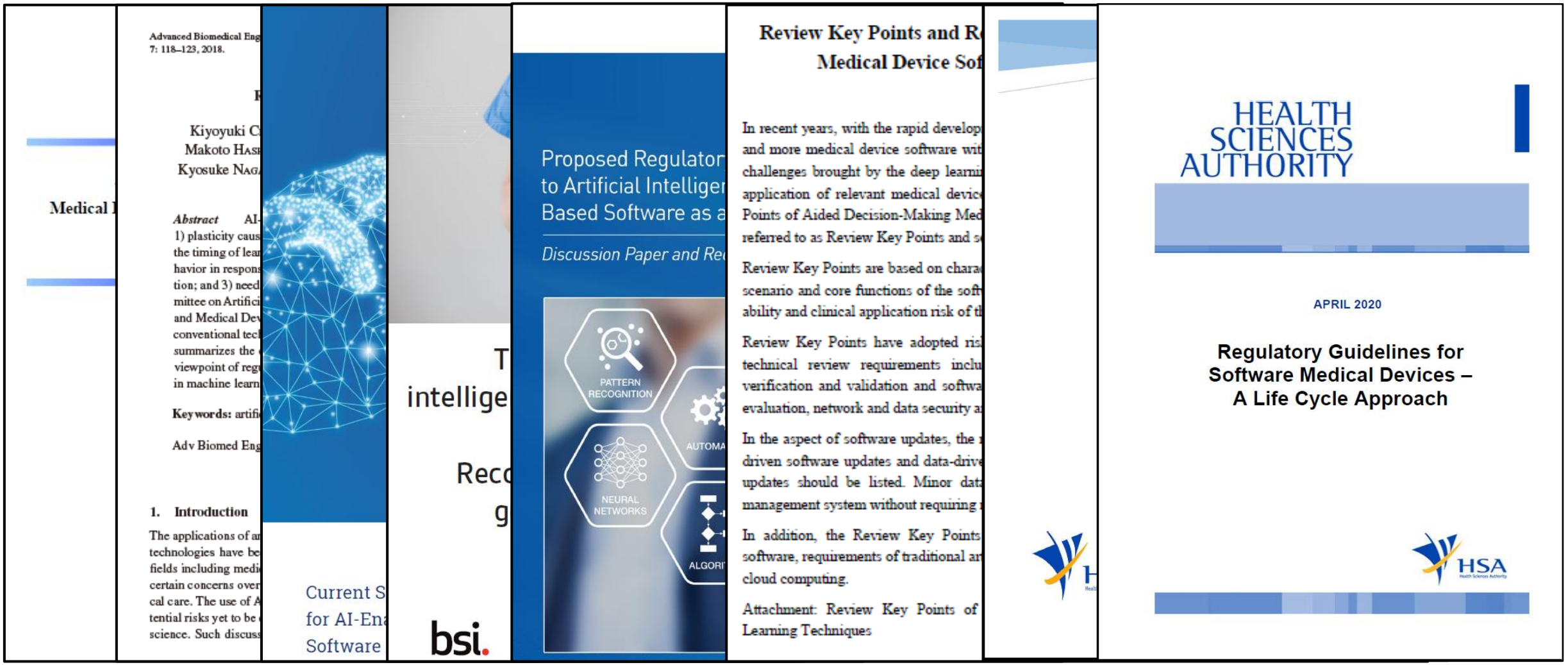


Global Organizations

WHO
IMDRF

Regulation of AI-Based Medical Device Software

Recent Publications



Alternative Approach for Modifications to AI Software

South Korea Big Data / AI Guidance

< Table 3. Version Control Method >

Item	Description (e.g.)	Control method
Major function change	Change of principle of operation, intended use, and performance (Performance change by the change of learning data is applicable only when the range of performance (accuracy) mentioned upon approval is deviated.)	Execution of variation approval
Simple change	Change of user screen (Graphic User Interface, GUI) design	Execution of variation approval
Minor change	Bug fixes, change of user screen (Graphic User Interface, GUI) color and menu location, etc.	Immediate report or annual report
Learning data change	Change of learning data within the range of performance (accuracy) mentioned upon approval	Manufacturer self-control

Source: *A Guideline for Approval Evaluation of Medical Device with Big Data and AI Technology Applied*, November 17, Medical Device Evaluation Department (South Korea)

Approach for Modifications to AI Software

NMPA Review Key Points Guidance

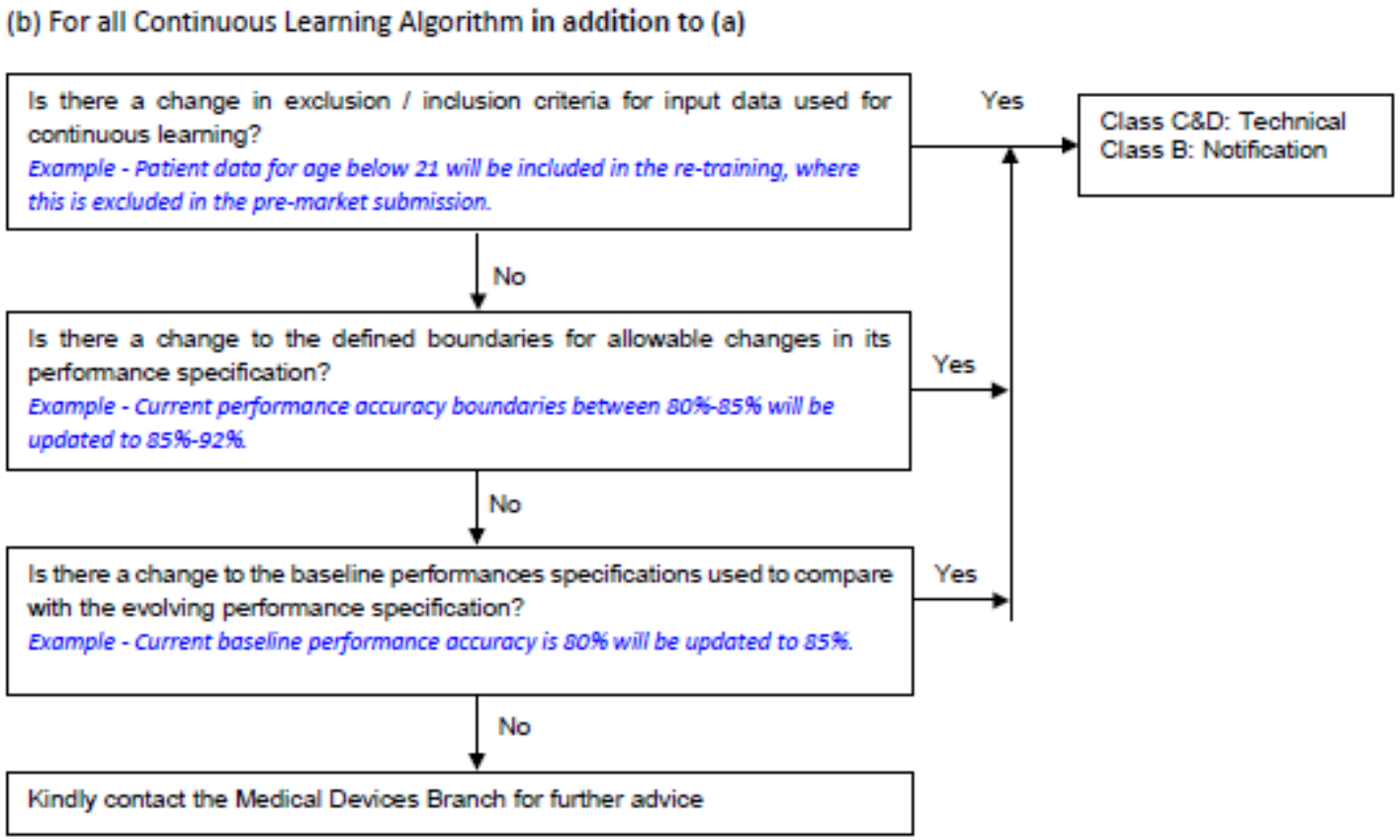
Major Software Updates	Minor Software Updates
Influences the safety or efficacy of the software	*Does not influence* the safety or efficacy of the software
Submission of *application for change approval*	Control performed through quality management system, *without need* to submit an *application for change approval*
Algorithm Driven	
Changes in the algorithm, algorithm structure, algorithm flow, etc.	
Data Driven	
Update due to increased training data	
Statistically significant changes in algorithm performance	*No statistically significant changes* in algorithm performance

Source: *Review Key Points and Relevant Instructions of Aided Decision-Making Medical Device Software Using Deep Learning Techniques*, National Medical Products Administration (China)

Approaches to Modifications for AI Software

HSA Regulatory Guidelines for Software Medical Devices

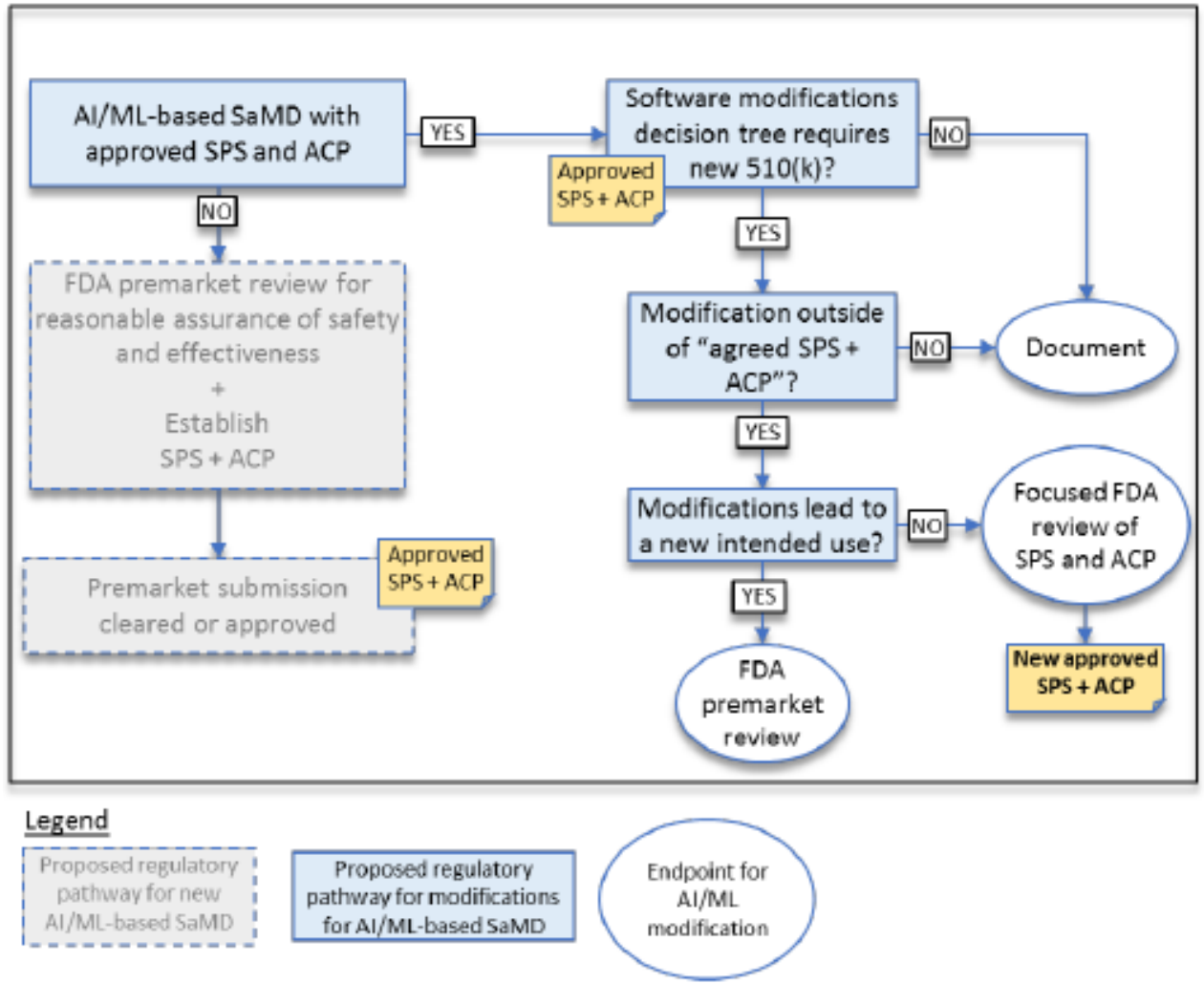
Modifications Flowchart Focused on Continuous Learning Algorithms



Source: *Regulatory Guidelines for Software Medical Devices – A Lifecycle Approach*, April 2020, Health Sciences Authority (Singapore)

Approaches to Modifications for AI SaMD

US FDA AI/ML-SaMD Discussion Paper



SaMD Pre-Specifications (SPS):

Outlines the changes the developer plans to achieve while the SaMD is in use.

Algorithm Change Protocol (ACP):

Methods the developer will utilize to achieve and appropriately control the risks of the anticipated types of modifications outlined in the SPS.

Source: *Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD),* US Food and Drug Administration.

Evolutions in the Regulation of Artificial Intelligence

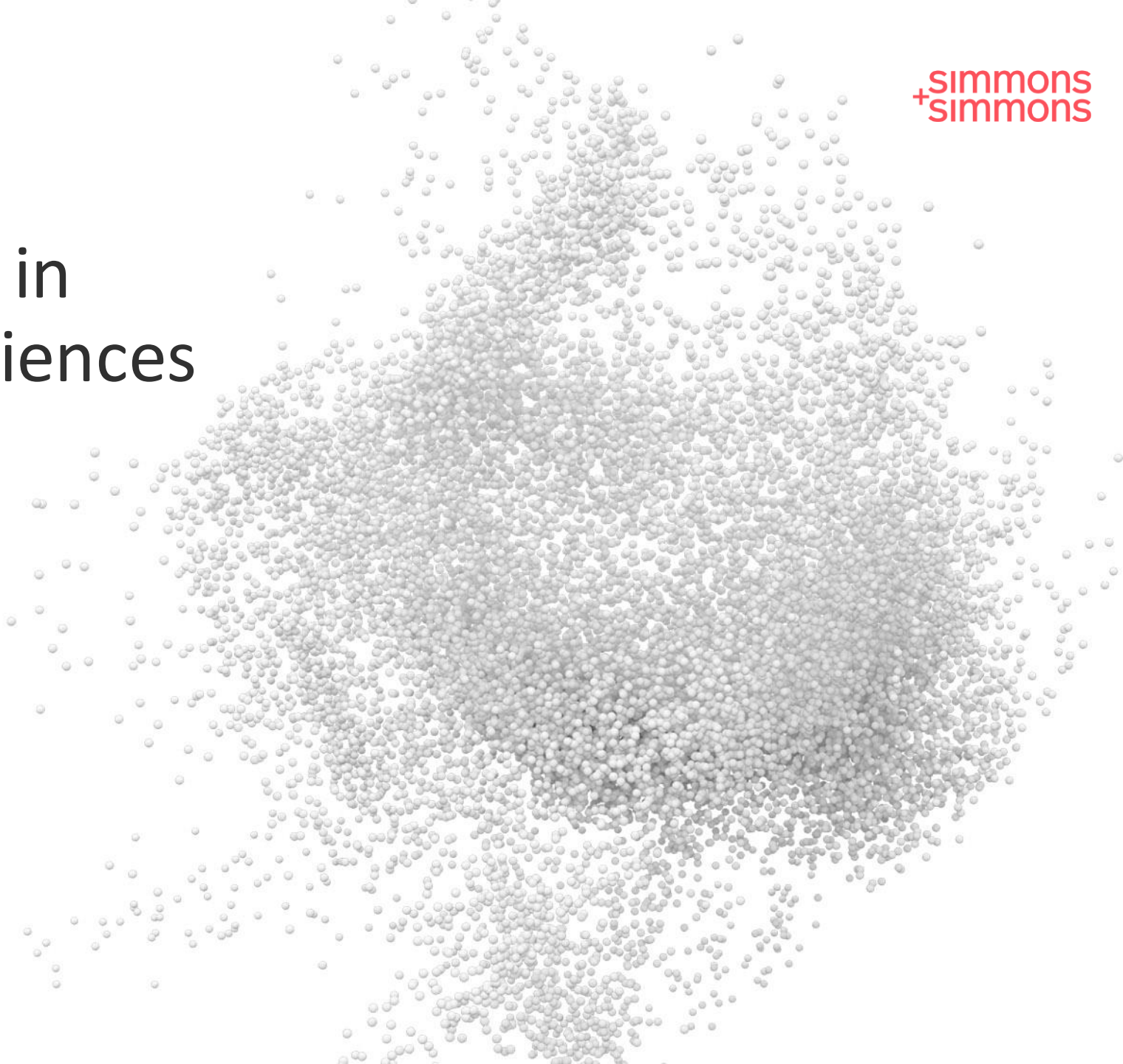
Key Takeaways

- ✓ There are different types of AI-Based Software as a Medical Device (SaMD), each posing its own unique risk profile and regulatory challenges. Such products need to be regulated based on their own risk.
- ✓ Existing SaMD frameworks, such as those developed by IMDRF, and existing standards, such as ISO 14971 and IEC 62304, should be leveraged, and adapted for the regulation of AI-Based SaMD products.
- ✓ Alternative regulatory pathways for AI-Based SaMD, particularly those that utilize Continuously Learning algorithms, should be explored that maintain device safety and effectiveness while enabling the innovative and iterative aspects of these products.

Doing now what patients need next

Artificial Intelligence

Legal & Ethical issues in healthcare and life sciences sector



AI and Regulatory

25 June 2020

What is AI?

What is AI?

Defining AI

- The Singapore Personal Data Protection Commission (**PDPC**) focuses on the association of tasks with human intelligence. It defines AI as:

  "…a set of technologies that seek to simulate human traits such as knowledge, reasoning, problem solving, perception, learning and planning, and, depending on the AI model, produce an output or decision…"

- The European Commission focuses on the ability of the system to act autonomously. It defines AI as:

  "…systems that display intelligent behaviour by analysing their environment and taking actions – with some degree of autonomy – to achieve specific goals."

- The UK Government Office for Science focuses on the analysis of data. It defines AI as:

  "…the analysis of data to model some aspect of the world. Inferences from these models are then used to predict and anticipate possible future events."

Ethical Issues

Why does AI attract legal and ethical risks?

Distinctive characteristics of AI

- Human distrust of technology
- The rate of technological change
- AI's capacity to act as a legal agent
- AI's capacity to make moral choices
- AI's ability to develop independently
- The impact of AI on fundamental rights
- The necessity of data in AI systems

Why does AI attract legal and ethical risks?

Main ethical challenges in healthcare

- Importance of proper informed consent and responsible use of AI technology, stressing that the potential harms related to the use of AI technology must be transparent to all involved
- AI in medicine also raises significant legal and ethical challenges. Several of these are concerns about privacy, discrimination, safety (including psychological harm) and the physician-patient relationship.

Regulation of AI

Regulation of AI

How is AI being regulated?

- The regulation of AI is still in its infancy, most current approaches provide general guidelines or principles for users of AI to follow.
- In Singapore, the PDPC has released a Model AI Governance Framework, which sets out two guiding principles, that AI should be:
  - Explainable, Transparent and Fair, and
  - Human-Centric.
- The Model AI Governance Framework also emphasises the importance of appropriate human involvement in decisions taken using AI.
- Compliance with the Model Framework is voluntary, but the principles articulated in it may form the basis of future regulation.

Regulation of AI

How does existing law apply to AI?

- AI is, of course, also subject to existing laws, such as:
  - Consumer protection law
  - Contract law
  - Data protection law
  - Tort law
  - Criminal law
- Compliance with such laws should be considered when AI systems are being developed and deployed.
- However, while these laws are, in principal, fully applicable to AI, they are often untested in the context of AI.

Explainability, Transparency & Fairness

Explainability

What does "explainability" mean and why is it important?

- The European Commission's "Ethics Guidelines for Trustworthy AI" emphasise trust in AI:

"Trustworthiness is a prerequisite for people and societies to develop, deploy and use AI systems"

- The Singapore PDPC has emphasised that "*the purpose of being able to explain predictions made by AI is to build understanding and trust*".
- An algorithm deployed in an AI solution is said to be explainable if how it functions and how it arrives at a particular prediction can be explained.
- The Singapore PDPC suggests providing individuals with counterfactuals or comparisons, such as:
  - "*You would have been approved if your average debt was 15% lower*"
  - "*These are users with similar profiles to yours that received a similar decision*"
- Remark: the "black-box" problem and diagnosis AI applications

Transparency

What is transparency?

- Individuals and organisations affected by AI systems should have sufficient information to understand how those systems affect them.
  - This ensures that individuals and organisations will be able to enforce their rights when they are affected by an AI system.
- In addition to ensuring AI decisions are explainable, organisations should:
  - **Traceability.** Document data and processes so that it is possible to trace the cause of errors.
  - **Information.** Clearly inform individuals when they are interacting with an AI and not a human being.
- This is best practice, although it may also become the basis of future regulation.

Fairness

Bias and discrimination – what is it and why is it an issue?

- "Bias" has many meanings but, in the context of AI and employment, it can mean:
  - Algorithmic bias, where the AI's decisions / output reflect the values or perspective of the humans that provided input.
  - Human bias (or prejudice), which is more subjective and refers to the potential for the AI's decisions / output to affect one individual in a different way to another individual where we, as humans, would treat them equally.
- In an medical context, human bias causes concern because it could lead to unfair patient outcomes.

Human aspect of AI

Human-Centricity

What is human-centric AI?

- The Singapore PDPC Model Framework suggests that AI solutions should be human-centric. This means that AI should be "*used to amplify human capabilities, the protection of the interests of human beings, including their **well-being** and **safety**, should be the primary considerations in the design, development and deployment of AI.*"
  - **Well-being**: Individuals, the broader society, the natural environment and other sentient beings should all be considered as stakeholders throughout the lifecycle of an AI system.
  - **Safety**: AI should be secure and resilient to attacks, such as hacking. Systems should produce reliable, reproducible results and there should be safeguards in case there are problems.
- Focus on human-centricity should help to mitigate the risks associated with AI deployment, but will also help develop individual trust in AI systems.

Examples of AI-related legal issues in the medical world

AI-related legal issues

Consumer protection law

- Consumer protection and product liability law is generally applicable to AI-based products (and services).
- However, AI has characteristics that make it difficult to apply existing law, such as:
  - Lack of transparency
  - Changing functionality (as a result of updates or machine learning)
  - Uncertain allocation of responsibility
  - Changing concept of safety (e.g., new cyber threats or personal security risks)
- Changes to consumer protection legislation may be made in future to address such AI-specific risks.
- The EU Committee on Internal Market and Consumer Protection has already called for product safety and services regulation to be updated to ensure that these rules are “fit for purpose” following the rise of AI and automated decision-making systems.

AI-related legal issues

Contract law – freedom of contract

- Many jurisdictions recognise the “freedom of contract” principle i.e. parties are free to enter into contracts on whatever terms they wish.
- Most jurisdictions impose limits on this principle. For example:
  - Where businesses enter into contracts with consumers.
  - Where businesses contract on standard terms.
  - Where parties include unfair terms, which may be regulated by law in certain jurisdictions.
- Contracts therefore allow commercial parties to allocate responsibility and risk. Careful consideration of this allocation is particularly important in the context of AI, which tends to have complex supply chains:
  - Should the developer of the AI system be liable, the user or data provider?
  - What if you add AI to a system or it changes autonomously?

AI-related legal issues

Contract law – mitigating the risks

- The risks associated with entering into a contract for the use of AI can be mitigated by:
  - The primary obligations, i.e. what each party is obliged to do (or not to do), should be clearly understood and defined in order to allocate risk and responsibility.
  - The circumstances in which an AI system could malfunction and what consequences should flow from any malfunction should be considered and reflected in the contract.
  - Parties should consider limiting the extent to which they can be liable for any harm caused by their AI system (including to a third party).
- It is important that the functioning of an AI system is well understood in order to ensure that any risks can be identified and addressed in contracts.

AI-related legal issues

Tort law – application to AI

- Tort law may apply where:
  - AI-based technology has malfunctioned;
  - Causing physical or financial harm to a person; and
  - Generally, where there is no contract or other public law regime which would apply.
- In order to establish that another person or entity is liable for the harm caused, tort law often asks the following questions:
  - Does that person owe a duty of care to the injured person?
  - Has there been a breach of that duty of care?
  - Has the breach caused a loss to the injured person?
- Where an AI-based technology has malfunctioned, these questions might not be easy to answer.

AI-related legal issues

Data protection law

- AI technologies are reliant on data. Where that data includes individuals personal data, data protection laws will apply.
- Organisations that develop or deploy AI systems that use individuals' personal data must consider data protection law.
- Common data protection requirements include:
  - Consent or lawful basis for using personal data
  - Minimising the amount of personal data held
  - Anonymising data that is processed (e.g. to train an AI)
  - Ensuring that AI models are resilient to cyber attacks

Any questions?

Key Contact

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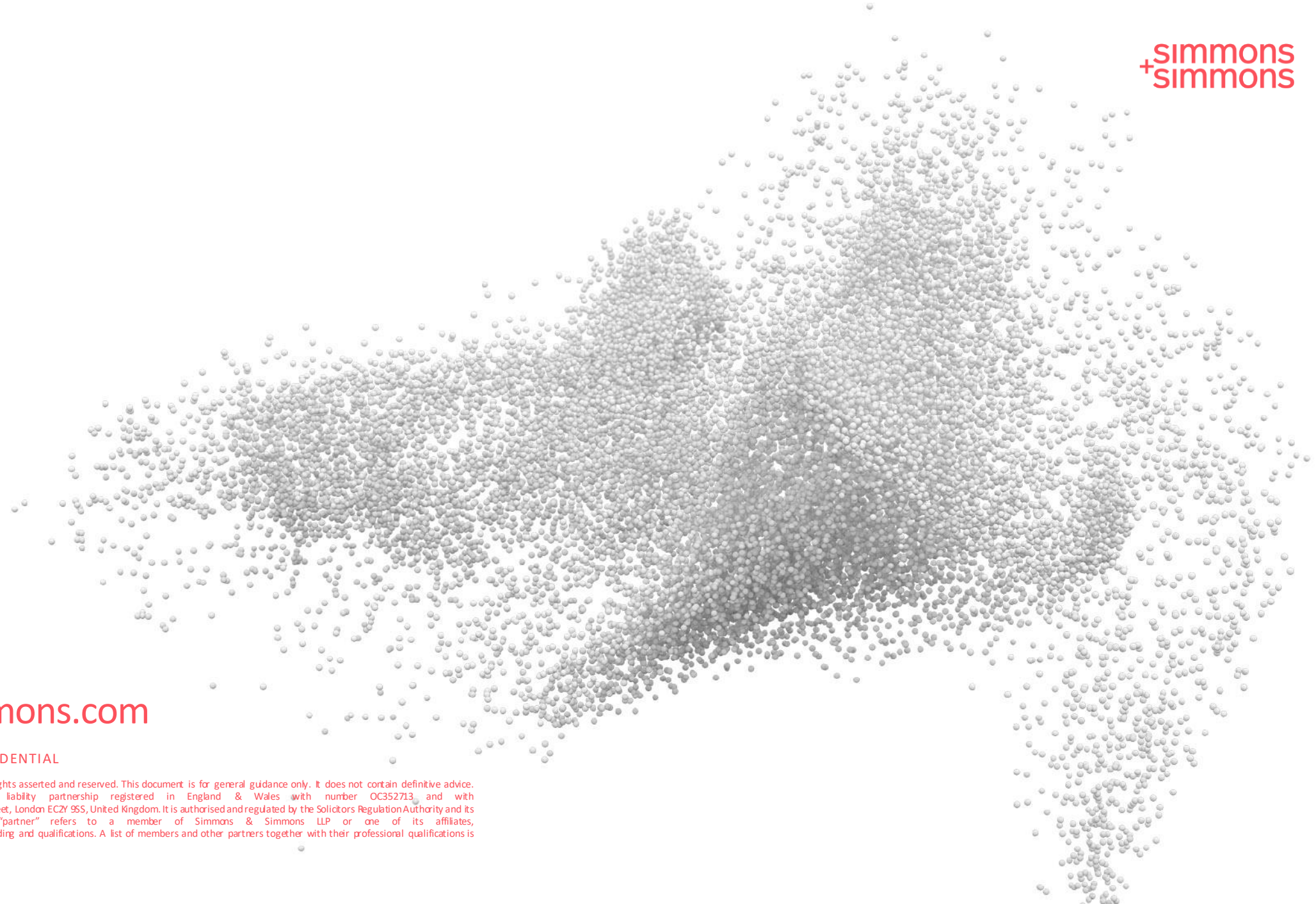
Lucas is dual qualified as a solicitor in England and Wales and an Avocat à la Cour in France.

Lucas specializes in complex commercial transactions in the tech sector with a strong focus in particular on medtech and biotech, including drafting complex distribution agreements as well as cross border dispute resolution and international arbitration in Europe, Africa and Asia.

Lucas is interested in the development of digital technology and disruption. He is a member of the think-tank Live with AI and part of its Blockchain & Health working group.



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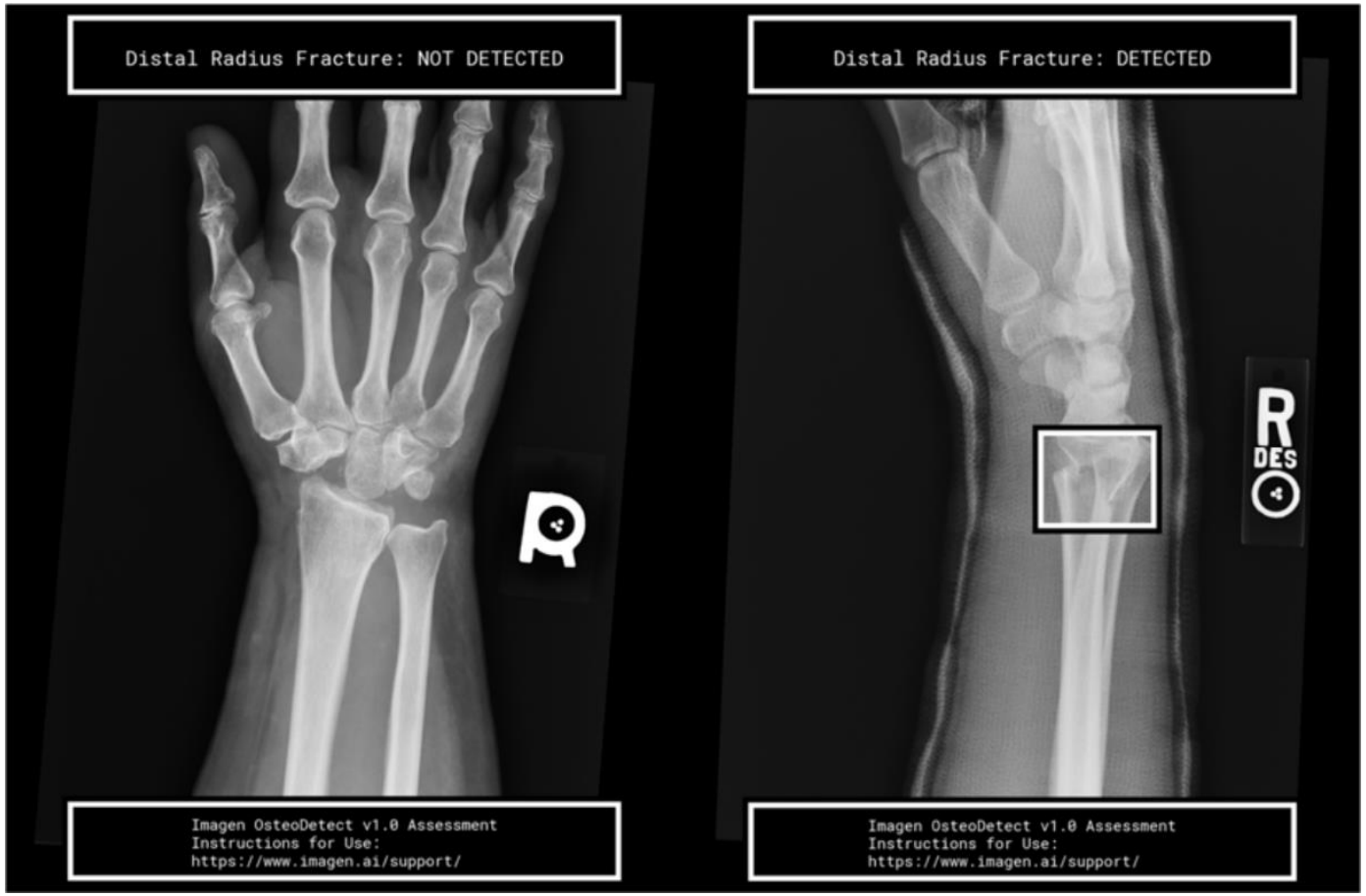
AI-Based SaMD Case Studies

Example of US FDA-Cleared ML-Based SaMD Product

Imagen Technologies – OsteoDetect



Intended Use Summary

OsteoDetect *analyzes wrist radiographs* using *machine learning* techniques to *identify and highlight distal radius fractures* during the review of posterior-anterior (PA) and lateral (LAT) radiographs of *adult wrists.*

Clinicians should *review* OsteoDetect *annotated images concurrently* with *original images* before making a final determination on a case. OsteoDetect is an *adjunct tool* and *does not replace the role of the clinician.*

Source: FDA De Novo Database, DEN180005

Example of US FDA-Cleared ML-Based SaMD Product

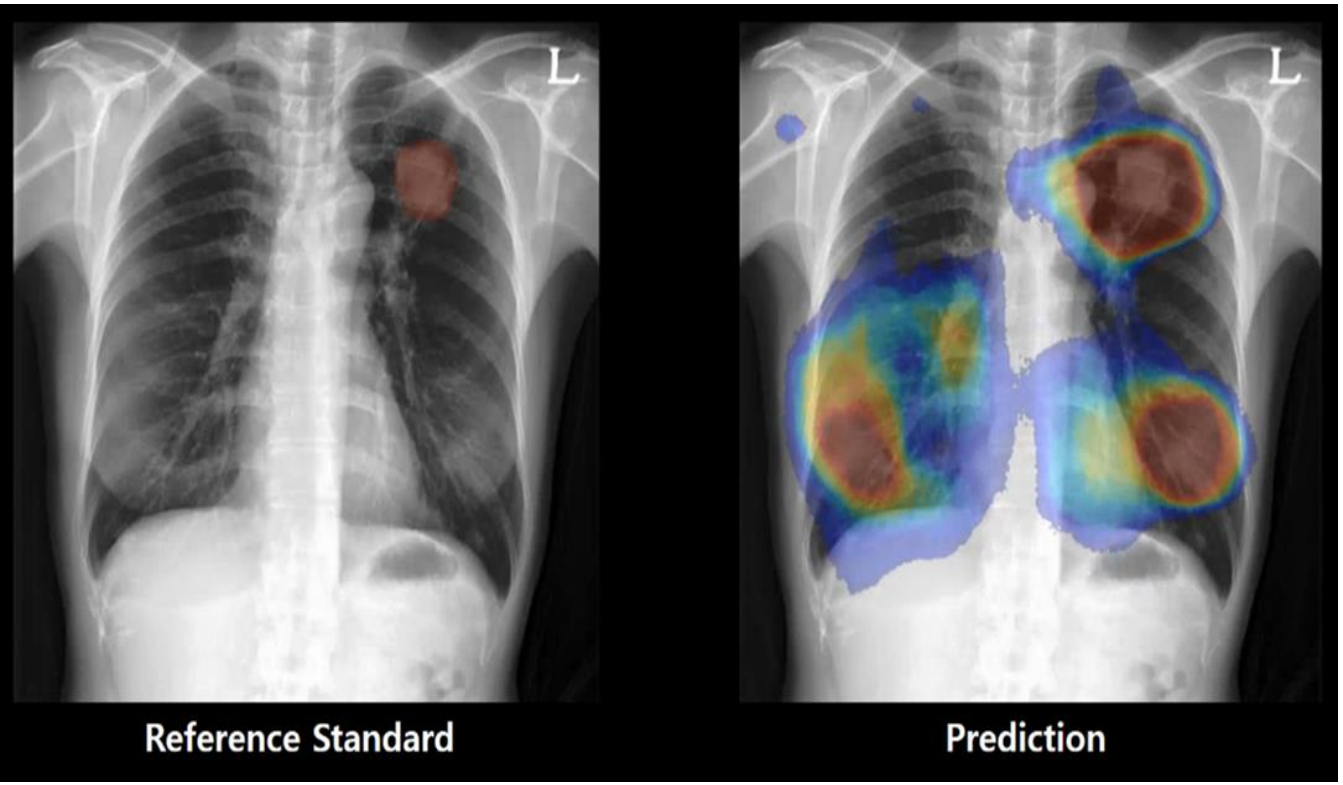
Imagen Technologies – OsteoDetect (continued)

- **Data Inputs:** PA and LAT wrist radiographs acquired with Philips Medical Systems DigitalDiagnost, Carestream Health DRX-1, and GE Discovery XR656.
- **Transparency/Interpretability:** Clinicians are able to review the OsteoDetect-annotated radiographs and the original, unaltered radiographs concurrently.
- **Product Risk:** Risks related to false positives, false negatives, device misuse, and device failure are mitigated by the software's use as an adjunctive tool.
- **Ethical Risk:** Human-centricity - Clinicians must remain at the center of the decision and must use the product to enhance the doctor-patient relationship
- **Legal issue:** Allocation of liability – OsteoDetect is a tool to help Clinicians provide a Diagnostic. Who is responsible in case of wrong diagnostic leading, for instance, to an invasive procedure?
- **Clinical Evaluation:**

Study 1	Study 2
Retrospective study	Retrospective study
1000 images (500 PA, 500 LAT) from three device types.	24 clinical readers assessing 200 cases both OsteoDetect-aided and OsteoDetect-unaided
Performance compared against three US board certified orthopedic hand surgeons	Performance compared against three US board certified orthopedic hand surgeons
Detection accuracy, localization accuracy, and generalizability (age group, sex, presence of a cast) assessed	Software-aided sensitivity and specificity of 0.803 and 0.914, respectively, vs. software-unaided sensitivity and specificity of 0.747 and 0.889
Sensitivity and specificity determined to be 0.921 and 0.902, respectively, with confounders not statistically affecting performance	

Example of MFDS-Cleared AI-Based SaMD Product

VUNO Med® Chest X-Ray



Intended Use (Abbreviated)

Vuno Med Chest X-ray is a *computer aided detection software* for *abnormality screening* on *chest radiography.*

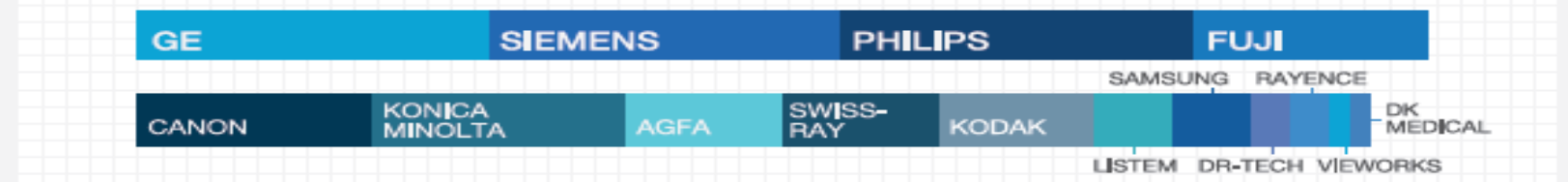
The algorithm was *trained* to find *nodules, pneumothorax, effusions, and interstitial opacities* that are commonly seen on chest x-ray images. The algorithm *classifies lesions as normal or abnormal* and highlights suspected abnormal regions.

Source: https://www.vuno.co/static/pdf/Chest_X-ray.pdf

Example of MFDS, Korea Cleared AI-Based Product

VUNO Med® Chest X-Ray (continued)

- **Data Inputs:** Algorithm is built and validated using X-ray images from multiple manufacturers:



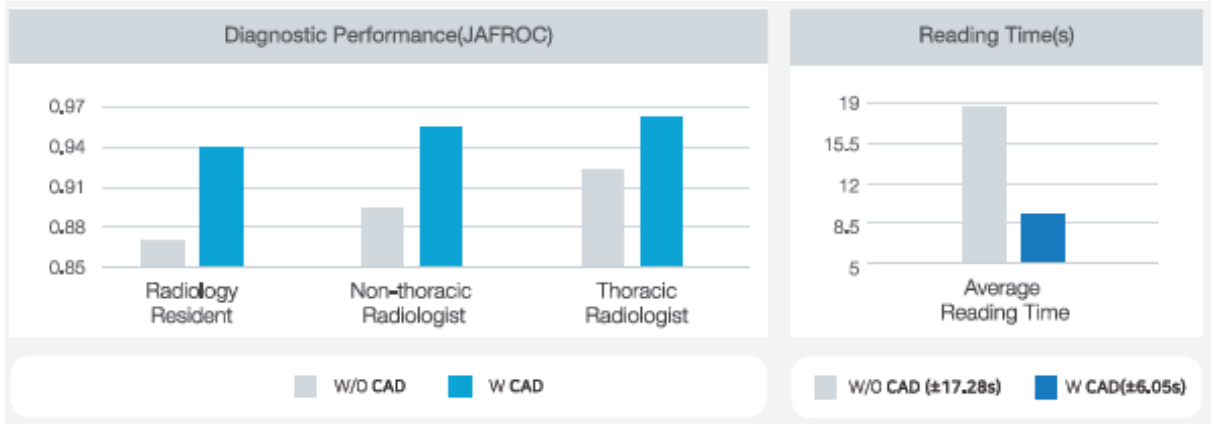
- **Transparency/Interpretability:** Physicians are able to independently review the X-rays and understand the source of the recommendations.

- **Ethical risk:** the algorithm and Clinicians must avoid bias to ensure fairness of VUNO Med® Chest X-Ray

- **Legal risk:** Awareness of data protection law implications – health data are considered sensible and should be handled with care – especially as for instance potential nodules and cancer cells can be identified by VUNO Med® Chest X-Ray

Clinical Evaluation & Performance Validation:

- Physicians participating in a randomized and cross-over study, conducted for MFDS approval, demonstrated more accurate diagnostic performance and shortened reading time when using VUNO Med Chest X-Ray SW.



Q&A

The voice of MedTech

Conclusions and next steps

- Next event of the Digital health committee: webinar on Indian Digital Health Blueprint on July 13th.

Please follow us on Linked in and expect more webinars in the coming weeks!

Thank you!

The voice of MedTech