Digital Health

Industry Perspective

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Topics

Useful Regulatory Frameworks for Digital Products

1 21st Century Cures Act and Regulatory Strategy

2 AI/ML-enabled Devices

3 Predetermined Change Control Plans

4 Global View

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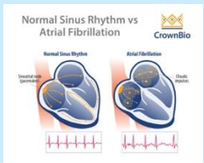
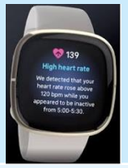
Is it a Medical Device?

	Fitbit ECG – Detection of Atrial Fibrillation	Fitbit Heart Rate
Does the intended use have a medical purpose?	 	
Intended use	To create, record, store, transfer, and display a single channel electrocardiogram (ECG) qualitatively similar to a Lead I ECG. The Fitbit ECG App determines the **presence of atrial fibrillation (AFib) or sinus rhythm** on a classifiable waveform.	Intended to display heart rate for informational purposes and provides informational alerts of low or high heart rates
Is it intended to **diagnose, cure, mitigate, treat, or prevent** disease?	Yes Afib, an irregular heart rhythm that increases the risk of serious complications like stroke	No
Is it intended to affect the structure or any function of the body?	No	No
Does it achieve its primary intended purpose by chemical action or by being metabolized?	No	No

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Device Software Functions

Categories and Regulatory Boundaries

Focus of Regulatory Oversight

Intended Use has a medical purpose

Could pose a risk to patient safety if the software malfunctions

SaMD

Examples:

Device Software Fu nne l device to control th data from the device.

Software that transforms a mobile platform into a regulated medical device: Apps that use sensors/displays/ attachments connected to a mobile platform to perform medical device functions

Patient Specific analysis
Diagnosis / Treatment
Active patient monitoring

May meet the definition of medical device

Enforcement discretion

Low Risk Software Functions

No Regulatory Requirements

Not a Medical Device

[Policy for Device Software Functions and Mobile Medical Applications]

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21st Century Cures Act

Simplifying Regulation of Software Functions

Software functions excluded from the device definition

(a) administrative functions.

(b) maintaining or encouraging a healthy lifestyle not related to a disease.

(c) electronic patient records.

(d) transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results and certain other related information.

(e) to provide recommendations to ***health care professionals*** for clinical decisions, where the ***user can independently review the basis of the recommendation.***

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Medical Device Data Systems

A Non-Device-MDDS is a software function solely intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected medical devices, which may or may not be intended for active patient monitoring:[5]

- The electronic transfer or exchange of medical device data. For example, this would include software that collects output from a ventilator about a patient's carbon dioxide level and transmits the information to a central patient data repository.
- The electronic storage and retrieval of medical device data. For example, software that stores historical blood pressure information for later review by a health care provider.
- The electronic conversion of medical device data from one format to another in accordance with a preset specification. For example, software that converts digital data generated by a pulse oximeter into a digital format that can be printed.
- The electronic display of medical device data, which may include certain secondary or remote displays to medical devices that solely display data and results. For example, software that displays a previously stored electrocardiogram for a particular patient.

Combining data to provide new insights, such as those related to correlation or causation, may push it out of MDDS

Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices

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Clinical Decision Support

Device or Not?

The Cures Act excludes certain CDS software functions

from device definition **if all four of these Criteria are met:**

Section 520(o)(1)(E) of the FD&C Act

- ❑ is **NOT intended to acquire, process, or analyze** a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system;
- ❑ intended for the purpose of **displaying, analyzing, or printing medical information about a patient or other medical information** (such as peer-reviewed clinical studies and clinical practice guidelines);
- ❑ intended for the purpose of **supporting or providing recommendations to a health care professional** about prevention, diagnosis, or treatment of a disease or condition; and
- ❑ intended for the purpose of enabling a health care professional to **independently review the basis** for such recommendations that such software presents so that it is **not the intent that such health care professional rely primarily** on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Clinical Decision Support Software

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Clinical Decision Support

Support or provide recommendations to an HCP

- ❑ Level of software automation.
- ❑ The time-critical nature of the HCP's decision making.

Non-Device CDS	Device CDS - Regulated
Enhance, inform, influence an HCP's decision making (e.g., list of general preventive, diagnostic, follow-up or treatment options).	Substitute, replace or direct the HCP's judgement.
Not intended to support time-critical decision making.	Condition specific alerts, active patient monitoring with time critical decision making. Alerts that trigger clinical intervention for patient safety.
No specific preventive, diagnostic or treatment output or directive.	**Medical purpose:** diagnose, treat, prevent, cure, mitigate disease or a condition. Specific follow-up directive. **Patient specific risk probability / signs** regarding a specific disease.

Automation Bias: Propensity of humans to over-rely on a suggestion from an automated system

- ❑ Can result in errors of
  - ❑ commission (following incorrect advice) or
  - ❑ omission (failing to act because of not being prompted to do so).

Software functions that provide support or recommendations to patients or caregivers are devices

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Multiple Function Devices

Multiple function device products have at least one device function that is the focus of FDA oversight and at least one “other function” that is not,

“Other function” is defined as a function

- that does not meet the definition of a device,
- a device function under enforcement discretion because of the low risk imposed to patients, or
- a device function that is not subject to premarket review (e.g., 510(k)-exempt).

The FDA does not review “other functions” of a multiple function device product; the FDA only assesses the impact of an “other function” on the safety and effectiveness of a device function-under-review

Multiple Function Device Products: Policy and Considerations

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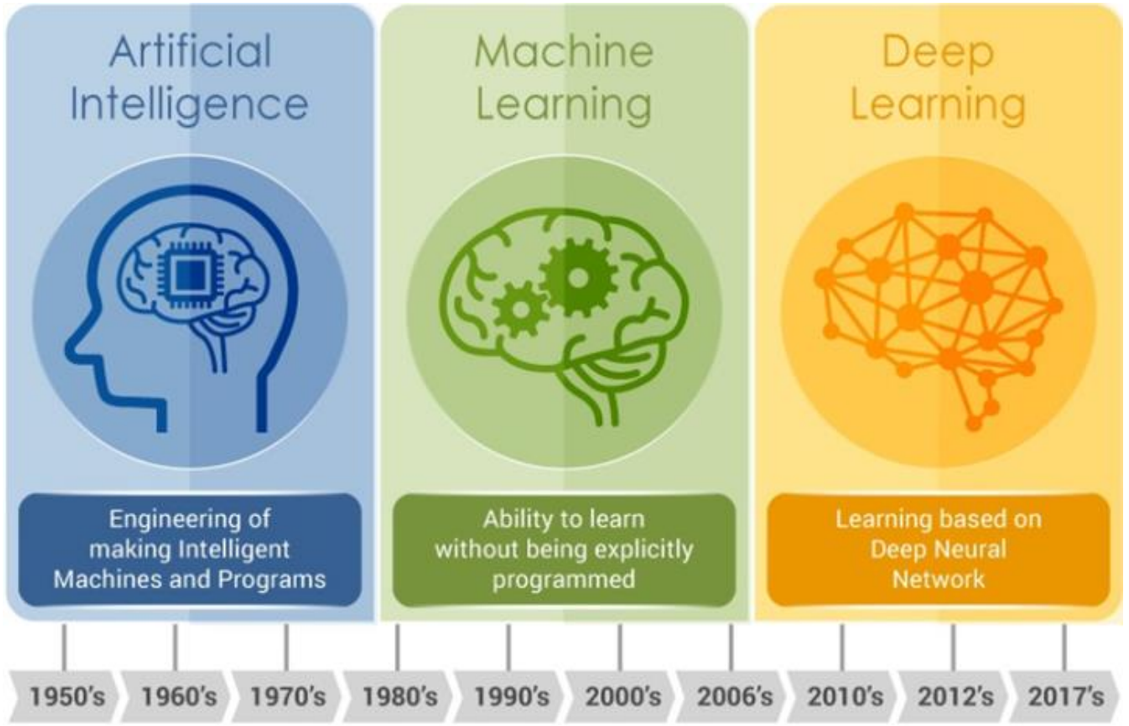
Artificial Intelligence and Machine Learning



Terminology
- AI Definition varies by jurisdiction
- Impact to regulatory assessments
- FDA Digital Health & Artificial Intelligence Glossary

Data
- AI/ML models are entirely dependent on integrity of data during model development

Locked vs. Adaptive
- Multitude of challenges with adaptive algorithms

Postmarket
- Ensure the model performs as expected in the field over time
- Predetermined Change Control Plans

Trust & Credibility
- Use explainability and transparency to build trust with clinicians and patients

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Data

Biases: Naturally occurring v.s. unintended

Naturally occurring biases may represent the true nature of a population (e.g. prevalence of a chronic condition within a specific population, sub-group).

Unintended biases arise from incomplete datasets, poor labelling, hidden variables etc. & are always negative resulting in inaccurate algorithmic decisions

Assessing for the presence and validity of biases

Compare the representativeness of the inputs to the intended outputs of the AI-MD.

Check for variable performance (in both outputs and error rates) of the AI across demographic sub-groups & assess the clinical relevance of any disparity.

Data Documentation

Credibility of the source of the dataset.
Period when the data set was compiled or updated.
Methods used to anonymize the data.
Accuracy of the dataset including accuracy of any annotated/labeled features.
Completeness of the dataset.
Medical relevance of the dataset.
Inclusion and exclusion criteria for data.
Justification for not overfitting (align too closely) and underfitting data (align not closely enough) to the data model being used.
Demographic representativeness (e.g. age, gender, ethnicity, sociodemographic stratum, location etc.).
Biases in the dataset & Biases in the algorithm.
Limitations to the intended use due to identified biases

Ensure that the training and test datasets are equally representative of the disease prevalence.

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Locked and Adaptive (unlocked) Algorithms

RISKS:

The ability of an algorithm to continuously learn and adapt during deployment could result in immediate updates to the inputs and outputs. The risks of such deployment include:

- **Inappropriate initialization** parameters can lead to divergence where the model does not operate at the most accurate points & affects the outputs.
- **Biased or unrepresentative input** data affecting algorithms on which the model is built.
- A possible **inability to fully validate updates to the algorithm** (in order to ensure clinical validity and accuracy) due to continuous learning abilities.
- **Abnormal behavior** (e.g. maliciously introduced data and/or end user manipulations (introducing rare yet valid and important data)

Safeguards to maintain safety, quality and efficacy:

- Deploy locked algorithms at user facilities while allowing the AI algorithm to continuously learn in parallel. Implement updates only when rigorous checks and validation have been conducted.
- Ensemble methods to enhance overall accuracy of AI-enabled devices. Mitigate risks of poor decisions, by adding decisions made by the re-trained device to an ensemble of other AI algorithms with validated performance.
- Ensure that the re-trained device and any subsequent versions are assigned new version numbers, are traceable, and can be reverted to a previous version when necessary.
- Controls to review the newly trained and deployed device
  - Automate validation
  - Record any input changes which lead to a drop in performance
  - Frequently review the input data to monitor and investigate model drift.
  - Incorporate appropriate triggers and escalation pathways should the AI-MD be no longer performing at or above the deployment baseline.

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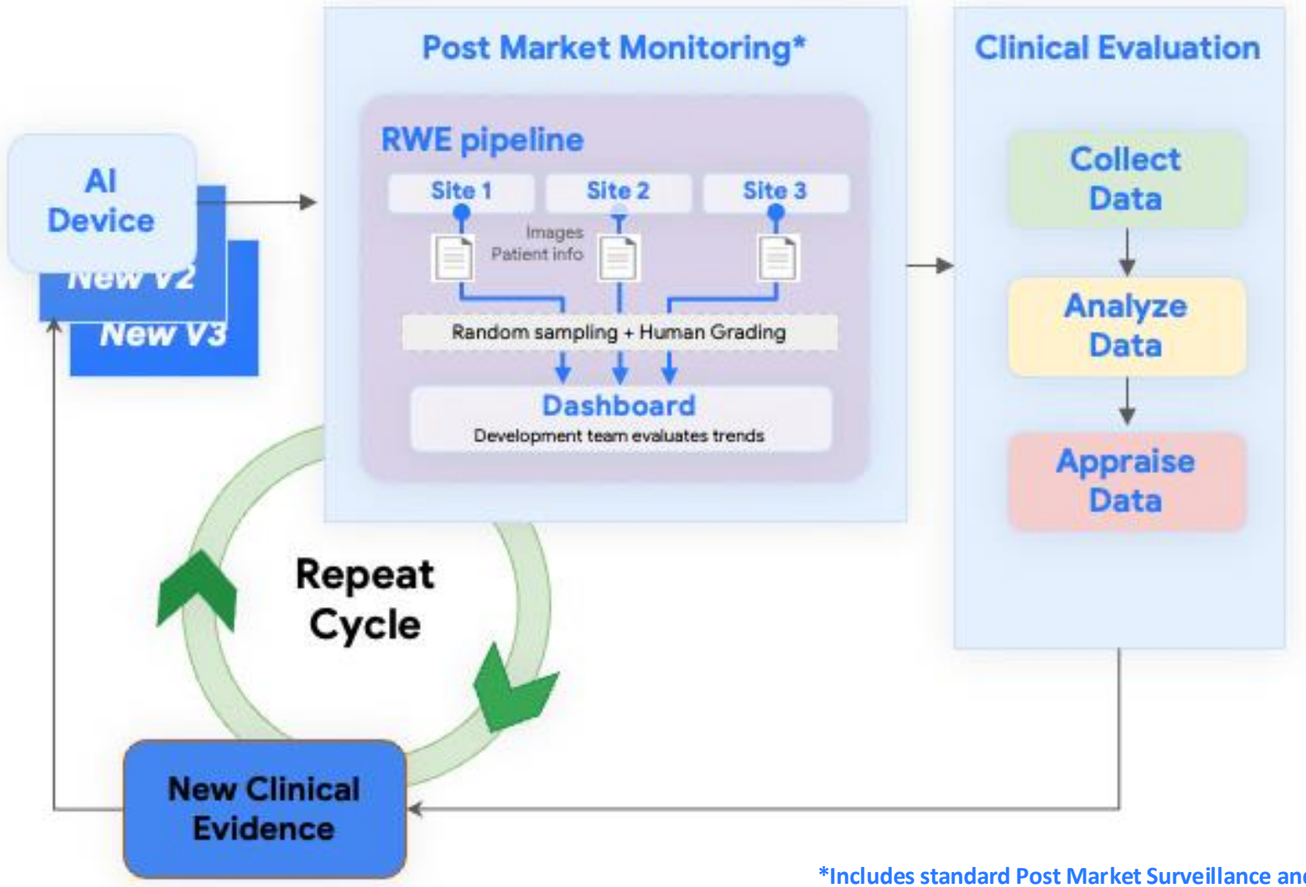
Postmarket Considerations – Courtesy of Google Health!

Intentional. Monitoring built in rather than an afterthought.

Embedded. Data collected during routine clinical care

Proactive vs reactive

Shared. Potential to aggregate across devices to develop a shared system to inform many stakeholders



*Includes standard Post Market Surveillance and Real World Evidence Pipeline

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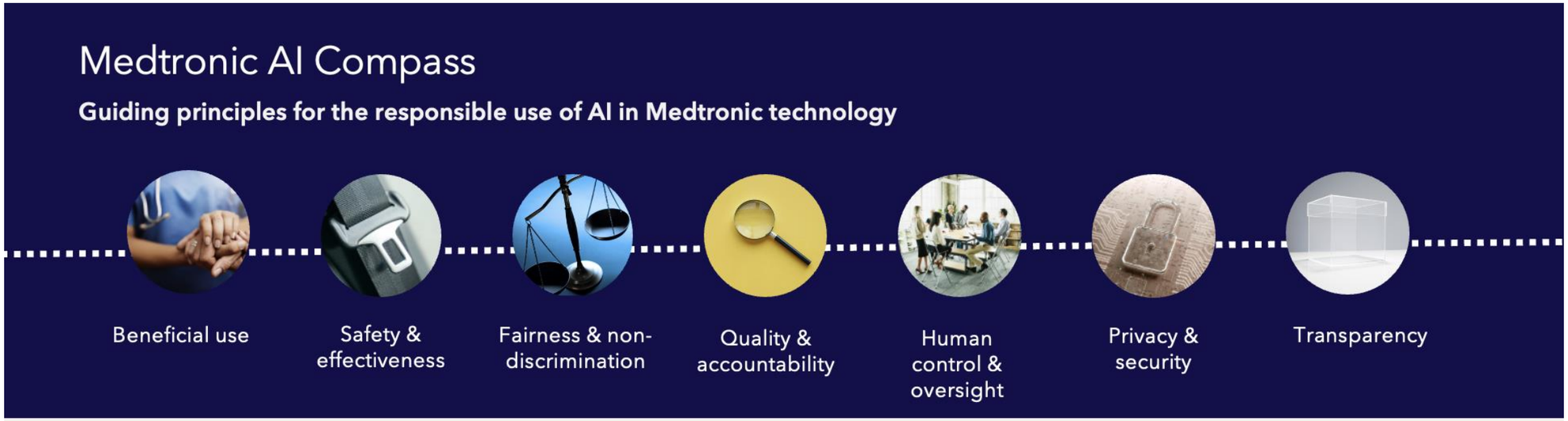
Trust & Credibility

A Medtronic Example



Purpose

- Affirm that the Medtronic Mission guides us to apply AI ethically and where it will make contributions to improve patient health outcomes and the conditions of patient care delivery
- Establish Medtronic as a bold leader in the application of AI to medical technologies
- Build understanding and trust through transparency with our users, including patients and healthcare providers.

View the Medtronic AI Compass

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U.S. Experience: Expanding use of PCCPs across all products

April 2019

FDA AI/ML-based SaMD discussion paper introduces PCCP concept

January 2021

FDA AI/ML-based SaMD Action Plan commits to draft guidance

June 2021

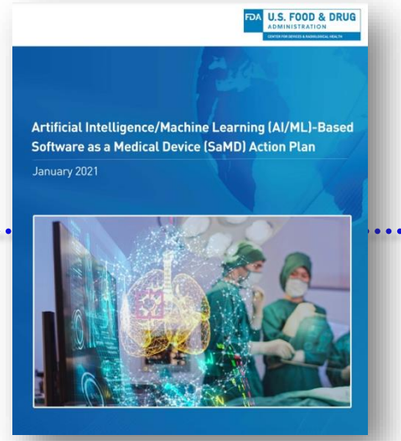
Several products received FDA authorization for PCCP from 2020-2022

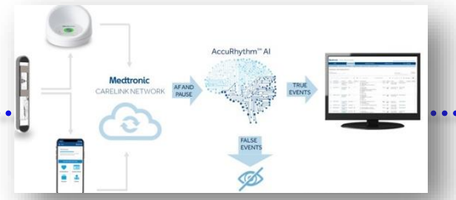
December 2022

Legislation expands voluntary use of PCCP across all premarket pathways and with *all* devices

April-Oct 2023

AI/ML PCCP draft guidance & PCCP Guiding Principles; Notifies of future PCCP draft guidance






Contains Nonbinding Recommendations
Draft – Not for Implementation
Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions
Draft Guidance for Industry and Food and Drug Administration Staff
DRAFT GUIDANCE
This draft guidance document is being distributed for comment purposes only.
Document issued on April 3, 2023.
U.S. FOOD & DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Office of Combination Products in the Office of the Commissioner

! PCCP no longer limited to AI/ML-enabled devices


U.S. FOOD & DRUG ADMINISTRATION
Health Canada Santé Canada
Medicines & Healthcare products Regulatory Agency
Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles
October 2023

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Predetermined Change Control Plans: Enabling more rapid improvements

Option to submit with initial premarket submission a plan for specific future postmarket modifications and methods to achieve and control any risks associated with those changes

PCCP components (from U.S. FDA guidance)

- Description of Modifications
- Modification Protocol
- Impact Assessment

After authorization, can make identified modifications while still ensuring safety & effectiveness of device

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Medtronic AccuRhythm AI ECG Classification Design Example

AccuRhythm AI ECG Classification System – Reduce Number of False Positives During Monitoring

Insertable cardiac monitor (ICM) system notifies clinic of observed arrhythmia events

- False episodes and associated follow-up increases burden, and sometimes concern, on patients unnecessarily
- AI-enabled tool designed to reduce number of false positives for most common episodes (AF and Pause), while maintaining sensitivity for true positive events

Design solution: **AccuRhythm AI™ ECG Classification System**

- Includes two new AI algorithms to adjudicate AF and Pause episodes detected by ICM
- Provides a layer of technology in the cloud to determine if device-collected arrhythmia episodes are false positives
- Preserves high sensitivity while reducing false positives
- Decreases data review burden on the clinician
- **Algorithms are locked**, not continuously learning / adapting in real-time

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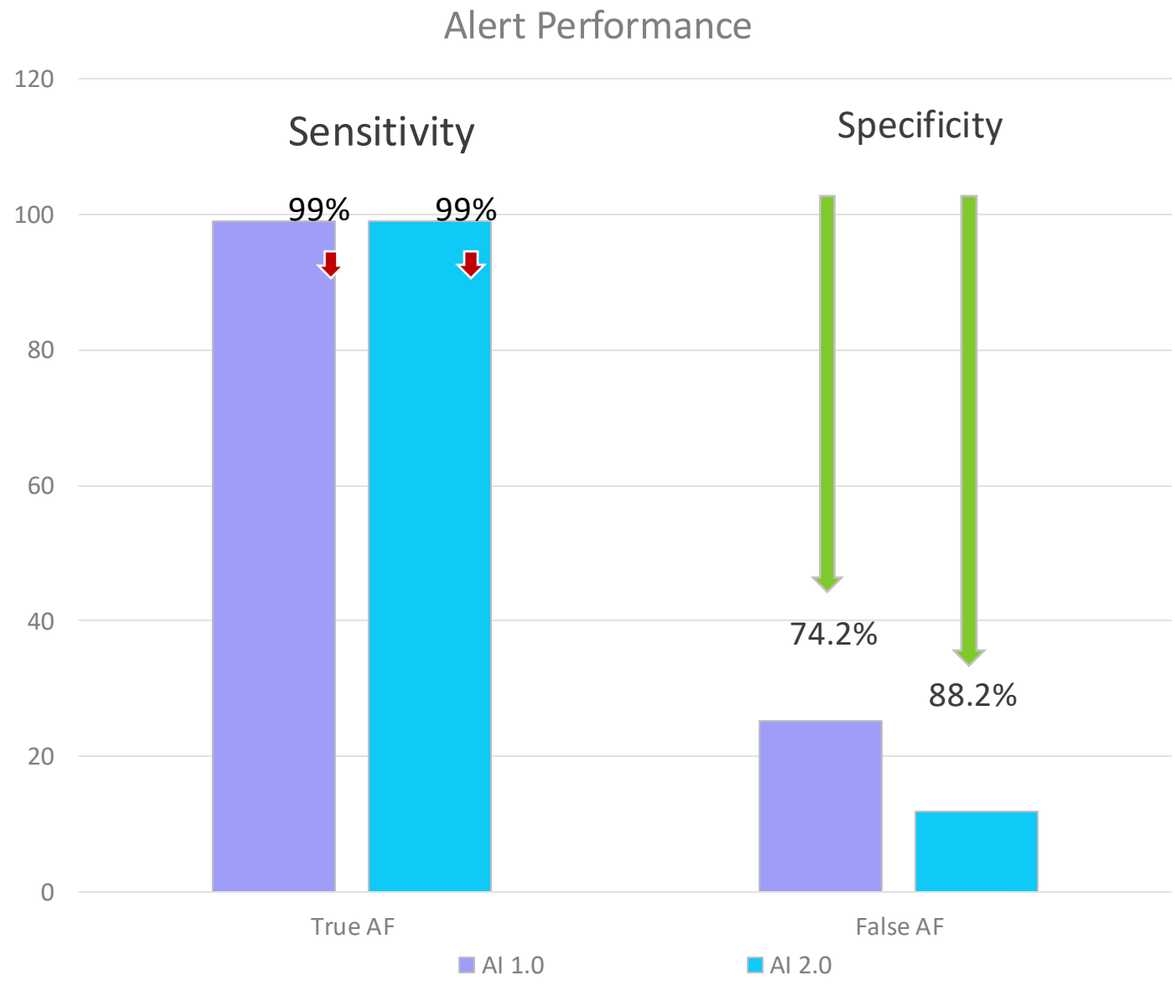
AccuRhythm AI Atrial Fibrillation Algorithm version 2.0 Example

Performance after following PCCP, including development and testing plan

Alert Level Performance

99% True AF Retained

88% False AF Suppressed



Radtke A, Hall M. AccuRhythm AI AF & Pause Algorithms White Paper. April 2023. Medtronic data on file.

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Global Regulatory Landscape

Medical Purpose: diagnose, treat, mitigate, prevent, cure, predict, prognose, monitor, manage, alleviate, modify anatomy

United States
FDA

Software exempted from device definition by the 21st Century Cures Act

(a) administrative functions

(b) maintaining or encouraging a healthy lifestyle not related to a disease.

(c) electronic patient records.

(d) transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results and certain other related information.

(e) to provide recommendations to ***health care professionals*** for clinical decisions, where the ***user can independently review the basis of the recommendation.***

MDSW

- Decision support software.
- A software module generating alarms based on the monitoring and analysis of patient specific physiological parameters.
- Telesurgery systems.
- Monitoring the performance of medical devices.
- IVD – Expert systems
- Interpretation of raw data.
- IMS that incorporate functions to support post-processing of images for diagnostics purposes.

Australia
TGA

Risk based approach to qualification

TGA has provided a comprehensive overview of software products that do not qualify as medical devices:

- Administrative support of healthcare facilities.
- Transferring storing converting formats
- Displaying laboratory test or other device data and results.

Excluded software products:

- Not subject to regulation by TGA.

Exempted Products:

- No pre-market review required but still monitored for safety & effectiveness.

e.g. electronic patient records software used for clinical workflow and support.

Japan
MHLW

Pharmaceutical & Medical Devices Act (PMDA) aligns with International Regulatory Best Practices

Exclusion examples:
- Software for health management.
- Software for transferring data.

Low risk CDS Qualification
Addressed by:

Multiple function devices
Addressed by:

Singapore
HSA

- Software is regulated as a medical device if its intended use falls under the definition of a medical device according to the Health products Act.
  - Investigation, detection, diagnosis, monitoring, treatment or management of any medical condition, disease, anatomy or physiological process
- A wellness product that is able to perform a medical device function (e.g., heart rate monitoring) requires "clarification statements" in the labeling to inform the users of the software's appropriate use.

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Key Takeaways

Thoughtful consideration of system architecture allows for better utilization of applicable software regulations and may lead to greater regulatory (and development) efficiencies.

AI is new and everyone is going through a learning curve together. A clear philosophy on your approach to AI will help your team develop and position your product for successful regulatory market authorization.

Although harmonization efforts are in play, software and AI regulations still vary widely by country. Optimizing for one may be at the expense of another.

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Thank you

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