Gastroenterology Articles   Gastroenterology

8-17-2021

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Saurabh Chawla

Jason Schairer
Henry Ford Health, jschair2@hfhs.org

Vladimir Kushnir

Yasmin Genevieve Hernandez-Barco

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Regulation of Artificial Intelligence-Based Applications in Gastroenterology

Saurabh Chawla, MD[1], Jason Schairer, MD[2], Vladimir Kushnir, MD[3] and Yasmin Genevieve Hernandez-Barco, MD[4]; ACG FDA-Related Matters Committee

The advances in artificial intelligence (AI) and machine learning (ML) technologies have created an explosion of research in AI-driven device development in gastroenterology. This is because machine learning can be reliably trained on and applied to diagnostic images captured during endoscopy. Recently, several randomized trials evaluating AI and ML for colon polyp detection have been published. Studies have been conducted evaluating the role of AI in dysplasia surveillance and other gastrointestinal (GI) disorders (1).

These technologies pose unique regulatory challenges because there is no precedent for the US Food and Drug Administration (FDA) to approve and regulate software which continually evolve and adapt based on real-world data.

In this article, we summarize the current concepts of the regulatory framework for medical software-assisted devices. We hope this would help the readers understand the processes involved before FDA approval for these devices.

EXISTING RISK STRATIFICATION OF DEVICES AND DEVICE REGULATORY PATHWAYS

A device is described as an instrument, reagent, or similar intended to diagnose or treat a disease or condition which does not fall under drug or biologics categories within the FDA (2). Medical devices are categorized in 3 classes (class I–III) based on the degree of risk they present. Class I devices are those that present minimal potential for harm (e.g., bandages and tongue depressors), whereas class III devices are those that are critical for sustaining or supporting life and/or present potential risk of illness or injury (e.g., pacemakers).

Based on the risk classification of the device, the intended use, and the presence of similar approved devices in the market, the device is then submitted to the FDA for approval, through 1 of 4 pathways (Table 1).

SOFTWARE AS A MEDICAL DEVICE

Software has become an integral part of most medical devices. Software can be used for manufacture or maintenance of a medical device (e.g., built-in diagnostic software which detects errors in machine operation) or can be integral for device functioning (also known as software in medical device [SiMD]). SiMD are part of the device hardware and are not regulated independently by the FDA. In 2013, the International Medical Device Regulators Forum, under the leadership of the FDA, defined a third category of medical device software as "software as a medical device (SaMD)" (3) (Figure 1). SaMD is intended to be used for 1 or more medical purposes without being part of a hardware medical device. These medical software are now ubiquitous and have functions ranging from delivering consolidated data output to influencing management decisions and are used in a large range of healthcare situations. Based on their role in decision-making and the impact of the software guidance, the FDA stratifies SaMD into 4 categories. Devices deemed to affect serious or critical health conditions are recommended to undergo independent review, whereas the lower category devices can be approved based on manufacturer's "self-declaration" (4) (Figure 2). A key tenant of conventional SaMDs has been the "locked algorithm" (Figure 3).

Locked algorithms provide the same result each time the same input is applied and does not change with use (4).

In these devices, the manufacturer can leverage the connectivity of the SaMD to monitor the safety, effectiveness, and the performance of SaMD. Any change in the algorithms require revalidation of the SaMD and resubmission for approval to the FDA. International Medical Device Regulators Forum and the FDA have outlined a pathway based on organization-based total product lifecycle approach, which would help streamline software precertification. It allows software regulation across its lifecycle from design and development to postmarket surveillance and software changes while monitoring the social-technical and information safety environment for the software (5). The FDA's Center for Devices and Radiological Health has also published guidance on approval for software changes to existing devices based on the risk to users or patients (4).

AI/ML BASED SaMD

There have been considerable recent advances in medical software development based on the concepts of AI and ML (6).

The FDA has approved several AI/ML-based SaMD with locked algorithms and changes beyond original market authorization requiring FDA premarket review. The FDA recognizes that the transformative potential of AI/ML-based SaMD is adaptive and can constantly evolve from real-world use and experience, leading to improved performance and expanded indications. It acknowledges that the current paradigm for medical device regulation was not designed for adaptive AI/ML technologies and has been developing a framework to provide appropriate regulatory oversight (7).

[1]Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA; [2]Henry Ford Hospital, Detroit, Michigan, USA; [3]Division of Gastroenterology, Washington University in St. Louis School of Medicine, St. Louis, Missouri, USA; [4]Division of Gastroenterology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA. **Correspondence:** Saurabh Chawla, MD. E-mail: saurabh.chawla@emory.edu.

Table 1. Different pathways utilized by US Food and Drug Administration for device approval

510(k) (premarket notification)	Used when submitted new device is "substantially equivalent" to a predicate device in terms of intended use, technological characteristics, and performance testing, as needed	Usually for class II and some class I devices. Important to note that most class I and some class II devices may be exempt from premarket submission
De novo classification request	Pathway to classify novel medical devices for which there are no similar approved devices but there exists general or specific control data demonstrating safety and effectiveness	Used for class I–III devices
Premarket approval (PMA)	Most stringent approval process, where the sponsor must provide high quality scientific evidence of the device's safety and efficacy	Usually used for class III devices
Humanitarian device exemption (HDE)	Pathway for approval of class III devices which are intended to benefit patients with rare diseases or conditions and do not have robust scientific evidence for support	Usually reserved for class III devices and require the device to be designated as Humanitarian Use Device (HUD) prior to submission

In April 2019, it published the discussion article "Proposed Regulatory Framework for Modifications to AI/ML-Based SaMD" and requested public feedback (7).This framework proposed a new total product lifecycle approach that would allow regulatory oversight while allowing for iterative improvement in the AI/ML-based SaMD and ensuring patient safety. The key components of this approach were as follows:

1. Establish clear expectations on quality systems and good ML practices from the device manufacturers to have assurance on their software development, testing, and performance monitoring throughout the lifecycle of the product.
2. Develop a predetermined change control plan to include anticipated modifications—SaMD Prespecifications based on retraining and model update strategy and Algorithm Change Protocol—used to implement changes in a controlled fashion,

which would determine need for regulatory approval of changes to the AI/ML-based SaMD.
3. Establish mechanisms that support transparency and real-world performance monitoring of these devices and allow the FDA to evaluate the product from premarket development through postmarket performance.

In a subsequent patient advisory committee meeting various concerns and limitations related to AI/ML technology such as generalizability and external validity of training data, algorithmic biases and opacity of data processing (also known as "black box" of AI), trustworthiness, consent, and skills degradation were discussed (8).

Based on the feedback from various stakeholders, the FDA released an AI/ML-based SaMD Action Plan in January 2021. It highlights steps to improve the regulatory plan for these devices (9). These include:
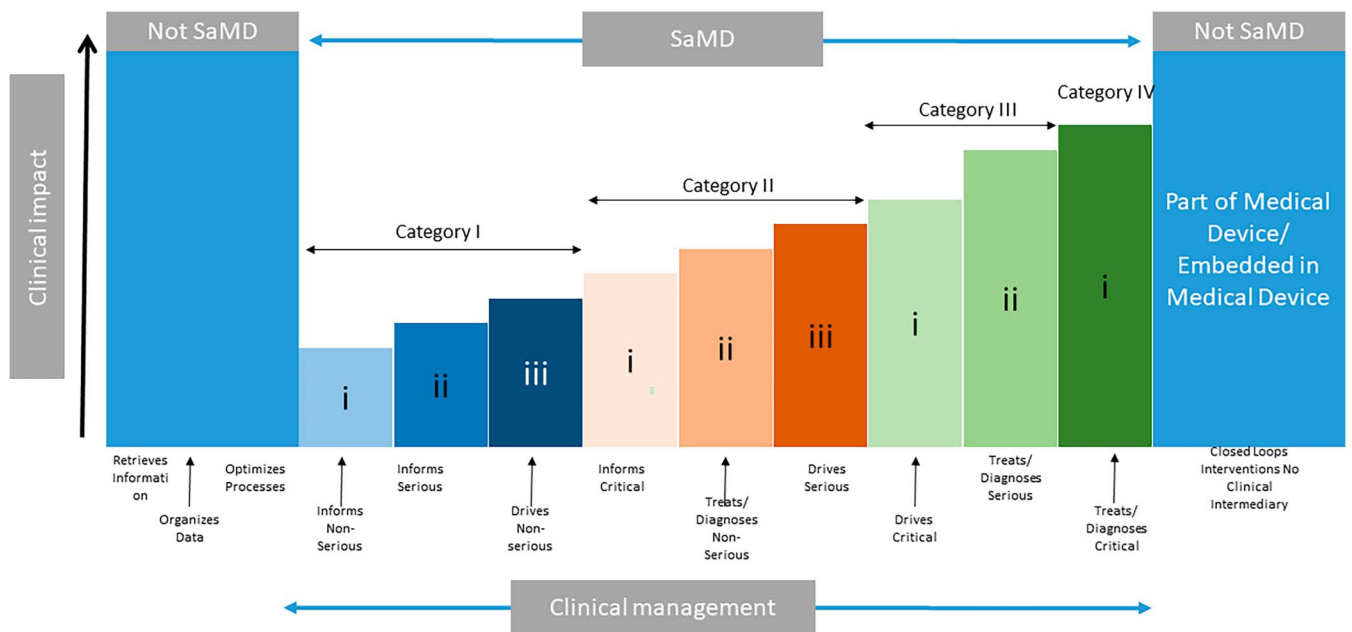
Figure 1. Definition and classification of traditional and software based medical devices. Source: FDA (8). FDA, US Food and Drug Administration; SaMD, software as a medical device.
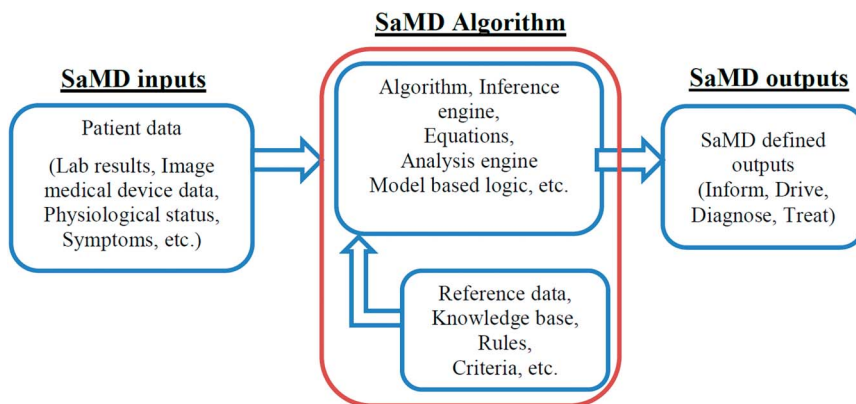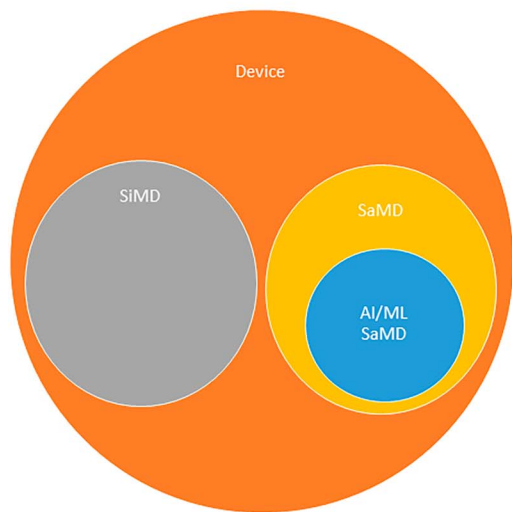
Figure 2. Framework for evaluation of software as a medical device (SaMD) for independent review. Categories I–IV are stratification of SaMD devices based on their healthcare impact from low to critical. Levels i–iii are risk stratification within each category from low to highest risk. Source: FDA (4). FDA, US Food and Drug Administration.

1. Issue a draft guidance on the Predetermined Change Control Plan to allow for modifications to AI/ML-based SaMD.
2. Develop consensus outcomes for good ML practices by collaborating with key stakeholders in the community, industry, and other regulatory bodies.
3. Hold a public workshop on device labelling to support transparency and enhance trust in AI/ML-based devices.
4. Recognize the risk of bias and generalizability because of limited training sets for AI/ML algorithms and support regulatory science efforts to develop methodology for the evaluation and improvement of ML algorithms.
5. Coordinate with stakeholders and other FDA programs to support pilot projects of real-world performance monitoring and its impact on AI/ML-based SaMD.

CASE STUDY

The FDA recently approved GI Genius, a AI/ML-based SaMD, which aids in polyp detection (10). This SaMD uses ML-based algorithms to identify and highlight polyps to aid the endoscopist in real time during a colonoscopy. Notably, this device has been studied as an aid in polyp detection and not in polyp characterization in a randomized clinical trial. It is not intended to guide the clinician in clinical management. Given its role as a diagnostic aid, this SaMD was deemed low to moderate risk by the FDA and approved through the *De Novo* classification pathway because there is no legally marketed predicate device to which this device can claim substantial equivalence. After this approval, subsequent generations of AI/ML SaMD for similar use could go through 510 (k) pathway if they demonstrated equivalence to this predicate device.

Device	'Medical device' means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means
Software in Medical Device (SiMD)	Software that is integral to the medical device hardware and is not regulated separate from the harware
Software as Medical Device (SaMD)	"Software as a Medical Device" (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.
Artificial Intelligence/Machine learning based Software as Medical Device (AI/ML SaMD)	SaMD that utilizes artificial intelligence/machine learning algorithms. These algorithms can be locked or adaptive.

Figure 3. Basic programming model for a locked algorithm SaMD. Source: FDA (4). FDA, US Food and Drug Administration.

APPLICATIONS FOR GASTROENTEROLOGY

At the time of submission of this manuscript several diagnostic GI AI/ML SaMD are being developed and undergoing rigorous clinical testing (1). These include AI/ML SaMD for classifying severity of colitis, detection of GI bleeding, detection of dysplasia etc. Most of these devices would be classified as diagnostic assist devices which would require the gastroenterologist to review the software generated alerts, and may therefore fall into the low-moderate risk category. These initial devices could be reviewed through *De Novo* classification with subsequent iterations being approved through the 510 (k) pathway (4).

CONCLUSIONS

The average time for approval of new devices through the *De Novo* and 510 (k) pathways is 6–8 months. The FDA recognizes the transformative role that AI/ML may play in the future of health care and also the inadequacies of conventional regulatory mechanisms to regulate this powerful technology. Through the Digital Health Innovation Action plan and SaMD action plans, the FDA is developing a flexible yet robust framework to regulate AI/ML SaMD that will help in monitoring the safety, effectiveness, and the performance of these devices and shorten the approval time for retraining these devices throughout their lifecycle (6).

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