Digital Health Devices (SaMD). From Concept to Regulatory Approval

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BACKGROUND

Digital Health has come to encompass many categories and is expanding its horizon without any clear boundary. This is due to rapid advances in App-based devices, information technology, data science, artificial intelligence and machine learning. Broadly, these categories are mobile Health, wearable devices, telehealth and telemedicine, and personalized medicine software. Stand-alone software Apps that qualify as a medical device are termed as Software as a Medical Device (SaMD) as opposed to traditional medical devices that may have both software and hardware or just the hardware. SCCR has experience in conducting clinical trials on SaMD such as optical sensors on smartwatch to detect irregular pulses. This trial enrolled 419,093 participants (Perez, MV *et al*; Turakhia *et al*).

Regulatory aspects of getting SaMD approved by the agency are complex. The process of design, development, manufacturing, and clinical evaluation is a lengthy process and must comply with safety and regulatory requirements (Sharma, BP, 2021). This presentation outlines key steps for the introduction of App-based devices to marketplace in compliance with IMDRF (International Medical Device Regulators Forum). The forum is chaired by US FDA and observed by WHO.

References:

- *Perez, MV et al*. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation, N Engl J Med 381:1909-1917, 2019
- *Turakhia et al.* Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study, American Heart Journal 207, 66-75, 2019

Sharma, BP. 21 CFR Part 11 Perspectives in SaMD and Software Systems, Paper presented at Advarra Onsemble Fall Conference 2021ue

METHODS

Before deciding on the method of SaMD design and clinical lot manufacturing, it is important to decide how an SaMD will be used for the healthcare decision to categorize the device by asking such questions: 1) Will the information be used to treat or diagnose a disease? 2) Will it drive/ inform clinical management? 3) Is it for informational purposes only?

Based on the category, a risk assessment is performed that feeds into generating software requirements for various functionalities of the device to be deployed, and risk mitigation to avoid external threats such as digital attack from spyware, adware, Trojans and viruses (Table 1, Table 2, Fig 1) .

Table 1: SAMD categorization

State of Healthcare Situation or Condition	Significance of information provided by SaMD to the healthcare decision		
	Treat or Diagnose	Drive Clinical Management	Inform Clinical Management
Critical	IV	III	II
Serious	III	II	I
Non-Serious	II	I	I

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Table 2: Risk Assessment and mitigation

- Accessibility- Can person with physical impairment access it?
- Cybersecurity- Data integrity/ security due to digital attack
- Interoperability- Can be used on any platform
- Data Integrity- Homeland security Advisory Notice to Medtronic
- Data security- Data breach, Internet-based updating system/ cloud security

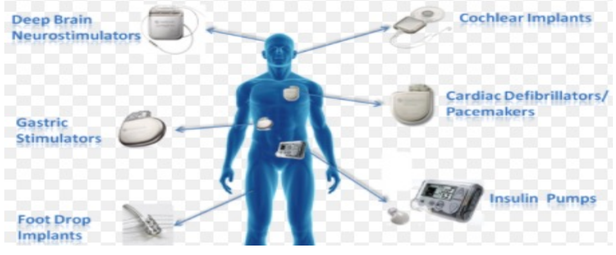

Fig 1: External threats to SAMD

RESULTS

Patient Data input and output algorithm

Core of design and development of SaMD is shown in Fig 2. For any data input there is an expected output. If the output is correct, then program routine for the test case is working as expected.

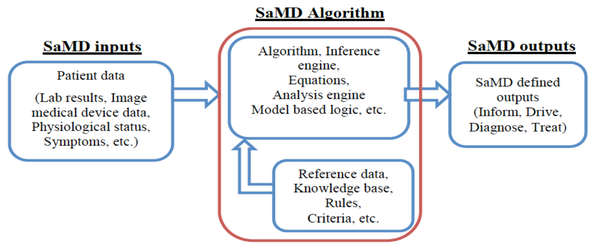

Fig 2: SaMD Design Control workflow

Total Product Life Cycle Approach for Design Control

To engage FDA early on, a company may participate in FDA Pre-certification pilot program that follows Total Product Life Cycle or TPLC approach. FDA started Software Pre-certification program in 2017 to reimagine its way of regulating digital health products. Many companies have participated since then such as Apple, Verily, Roche to name a few. Participation really helps as it provides guidance and learning experience to design, develop and deploy SaMD successfully. FDA can be a tremendous help when you have questions for the TPLC process. However, please note that FDA is also learning and some

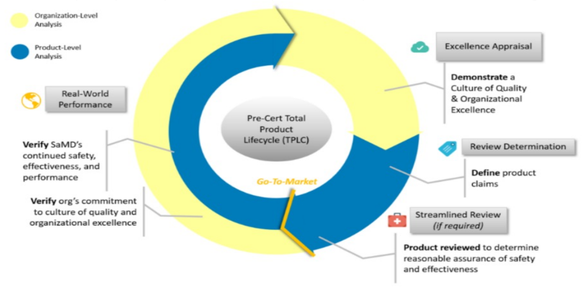

Fig 3: FDA SaMD pre-certification program and TPLC

Clinical Evaluation

Clinical evaluation determines that output of a SaMD is clinically valid and is reliable and predictable. Clinical evaluation is systemic and planned process to generate, collect, and assess clinical data to generate clinical evidence verifying the clinical association and the performance metrics of an SaMD as intended by the manufacturer. Being able to generate evidence to demonstrate the valid clinical association, analytical validation, and clinical validation of the SaMD is key to establishing the device's value for users. This can be accomplished by performing clinical association, analytical validation, and clinical validation of the device (Table 3) .

Validation is driven by the SaMD category and is risk-based. Category I (low or no risk) SaMD provide some information to users such as walking speed, heart rate, blood pressure whereas Category IV (high risk) provide data to physicians to diagnose and make clinical decision; for example, data to screen for mutable pathogens, e.g., COVID-19. Rigor of validation will depend on the SaMD category.

Analytical validation of SaMD for accuracy, repeatability and reproducibility provides results that relate to functionality of the device. Testing provides the assurance that user is getting accurate result each time the device is used compared to well established methods used in hospitals and clinics.

Clinical validation addresses the question, "Does SaMD generate clinically relevant output for the diagnosis, treatment, or prediction of treatment response? This is performed in the context of clinical care to determine sensitivity and specificity by selecting statistically significant number of subjects in the target population needed to treat or needed to harm the patient based on odd ratio and confidence intervals. This is done both pre- and post-market to understand the SaMD in the target population for its intended use (Table 3, Table 4).

① Valid Clinical Association	② Analytical Validation	③ 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?

Category IV
- SAMD for diagnostic image analysis for making treatment decision of acute stroke
- SAMD data to screen for mutable pathogens, e.g., COVID-19

Category III
- SAMD for radiation treatment planning system
- SAMD providing info by taking pictures and monitoring growth to diagnose skin lesion

Category II
- SAMD that analyzes heart rate data for a clinician to aid in diagnosis of arrhythmia
- SAMD data for predicting risk score for developing stroke or heart disease

Category I
- SAMD providing walking speed, heart rate, blood pressure info
- SAMD image data info that guides next diagnostic action of astigmatism

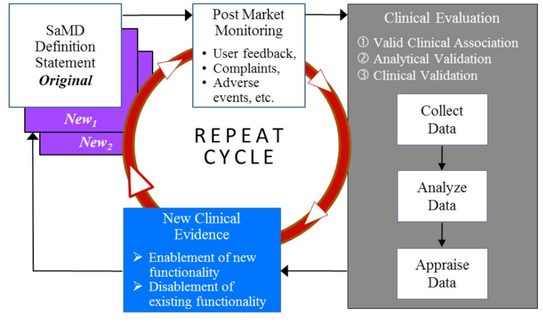

Fig 4: SAMD performance

Real World Performance of SAMD

Continuous learning of the SaMD from the real-world data is important for safety, efficacy and its performance. This helps in adding future functionality for label extension or even delete functions that is not useful anymore. This can help with ongoing clinical evidence generation and new research publications that support the clinical association of SaMD output to clinical condition or direct end- user feedback. Based on data, SaMD definition statement may also change. In this case, Manufacturer shall update the clinical evaluation and generate new definition statement. However, new definition statement may be subject to new regulatory requirement

Tips for FDA Approval- SaMD

- Engage FDA early
- Start IDE
- If not able to classify, let FDA classify it
- Maintain Design History Files
- Submit 510(k) or make *de novo* submission

CONCLUSIONS

Digital health has brought a new paradigm shift in healthcare management. SaMD provides unique features that extend beyond those of the traditional medical devices or hardware. Unlike other devices, SaMD can leverage technology and connectivity to devices as well as people that can continuously monitor safety, effectiveness, and performance of the device from comfort of their homes. Risk-based clinical evaluation and validation are key to success. Software developers and quality & compliance personnel should work together to deploy the device to ensure the device is safe and compliant to all required regulations. Continuous improvements by collecting real-world performance data are crucial to extend SaMD functionality overtime and/or delete functionality that do not work or fit the healthcare needs. Following TPLC for design, development in accordance with IMDRF and US FDA QMS is sure path for successful approval of an SaMD.

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