Emerging Trends in ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING DRIVEN SOFTWARE AS A MEDICAL DEVICE (SaMD): From Innovations to Regulatory Landscapes

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Abstract:
The emergence of artificial intelligence (AI) in the healthcare industry has increased novel health technology with promising features. SaMD is a software capable of performing different functions like diagnosis, treatment, monitoring, and prevention, even without the need for other hardware. AI/ML devices work on various algorithms, one is a locked algorithm that consistently provides the same output for a particular input, While the other is an adaptive algorithm that constantly updates its data concerning the real world to give more precise results. UTAUT model is a type of model that is also used by SaMD medical devices, this model works on various principles which are discussed in the article. A SaMD needs to be approved first before being marketed, there are various regulations associated with the approval and marketing of a SaMD, and different countries have different regulations to comply with. In this article, various regulations on marketing and approval of SaMD of different countries are also covered. A SaMD software known as "DIGITAL TWIN "is a software that creates a twin of a physical entity in the digital world, it helps healthcare people rule out diseases, choose treatment, and avoid potential risks. The paper concludes with two main concepts: first, the regulatory framework which gives an insight into how SaMD are marketed in various countries, and second an innovation of SaMD known as the digital twin which includes its basic concepts, need for a digital twin, and their regulations.

Keywords: Software, Healthcare, Devices, Algorithm, Regulations,Treatment, SaMD, Twin Model, Artificial Intelligence.

1. INTRODUCTION

Advances in all healthcare directions have made medical devices an integral part of our day-to-day lives. Medical devices now go mutual with drugs for sustaining a healthy lifestyle. Around 2 million types of different medical devices are available globally in today's time. SaMD is a type of medical device added to the healthcare industry to unlock new opportunities in healthcare.

The software can withhold the history of a patient's data such as blood sugar and blood pressure and an assemblage of that history can notify future decisions about patient care and therapy and can reduce the workload of the doctors and nurses. This technological advancement is remodelling the healthcare industry. There is an upsurge in the inclination towards expanding AI-ML-based software in the field.

In the meantime, there is increasing attention towards physical tele-monitoring of patient vitals daily, AI-ML can help to transform that data to inform clinical factors. These applications can include diagnosis based on AI-driven digital image processing, recognition of disease patterns, prescriptions, and patient brand-seeking behaviour regarding medicines. Therefore, AI-ML technology which is converted into a medical device can help or assist healthcare providers in decision making delivery of care, and clinical outcomes.

Artificial intelligence is a wide field of study that aims to design and understand the system that portrays characteristics of intelligence while machine learning is an element of AI that narrates how algorithms and models can help computer systems in gradually improve their performances.

In healthcare industries, artificial intelligence and machine learning (AI-ML) governed devices seek to improve patient care by discovering new insights from big data which is generated by an individual patient and aggregated experience of other patients.

AI can be defined as the science of producing intelligent machines, chiefly intelligent computer programs, however, there is no proper definition of AI and it can accumulate different techniques, for instance; Machine Learning, Statistical Methods, or expert systems that essentially depend on decision roles. In addition, the various techniques can overlap, especially ML and Statistical methods.

When planned to diagnose, treat, or prevent health-related issues, AI-ML-based software can be defined as a medical device under the Food, Drug, and Cosmetic Act (in the USA) and Counsell Directive 93/42/EEC (in the EU). AI-ML devices work on an imagining system that uses algorithms to give diagnostic output for various diseases.

The regulations and approvals of SaMD medical devices are quite contrasting in the USA and EU. There is no clear regulatory pathway for SaMD medical devices in the USA and EU. On the contrary, based on the risk of the devices, the FDA approves medical devices through main three streams i.e., pre-market approval, de-novo pre-market review, and 510(k) pathway.

1.1. What is a SaMD medical device?

SaMD is specialized software that performs medical functions while the software may be incorporated into a small piece of hardware. Also, it is a software that performs the medical functions. The International Medical Device Regulator Forum (IMDRF), describes SaMD as software that may work on non-medical-purpose computing platforms. It can be used in combination with other products, along with medical devices.

SaMD software is a medical device, which is capable of executing various medical functions such as diagnosis, treatment, monitoring, and prevention of the disease.

Software that is an important function of hardware such as software that helps Magnetic Resonance Imaging (MRI) magnet turn or control an X-ray panel, is not a SaMD. Nor is a device that primarily retrieves information, organizes data or optimizes processes.

SaMD	Not SaMD
Software that can determine the proper drug dose for a patient, given personalised patient data.	Software that operates a pacemaker
Software that can detect and diagnose a stroke by analysing MRI images	Software that drives or controls and infusion pump's motors
Software that can track the size of a mole over time and determine the risk of melanoma	Electronic health record system
Software that draws on data from other digital devise to determine risk factors associated with epileptic seizures	Software in the machines that assemble medical devices
Eg: Software that collects a large amount of data from multiple sources (x-rays, scans, etc.) and transforms that data into 3D models. These models can then be used by doctors for diagnosing or developing a treatment plan.	Eg: Software that operates imaging devices, such as software that rotates the magnets in an MRI or activates the control panel in an X-ray machine.

1.2. Role of SaMD in medical settings

1.2.1. Disease management

It helps doctors and patients to keep a watch on health data and to modify treatment in a personalized manner.

1.2.2. Recognising medical condition

It can help with customized plans for treatment and reducing the gap between diagnosis and treatment.

1.2.3. Disease management

It helps doctors and patients to keep a tab on health data.

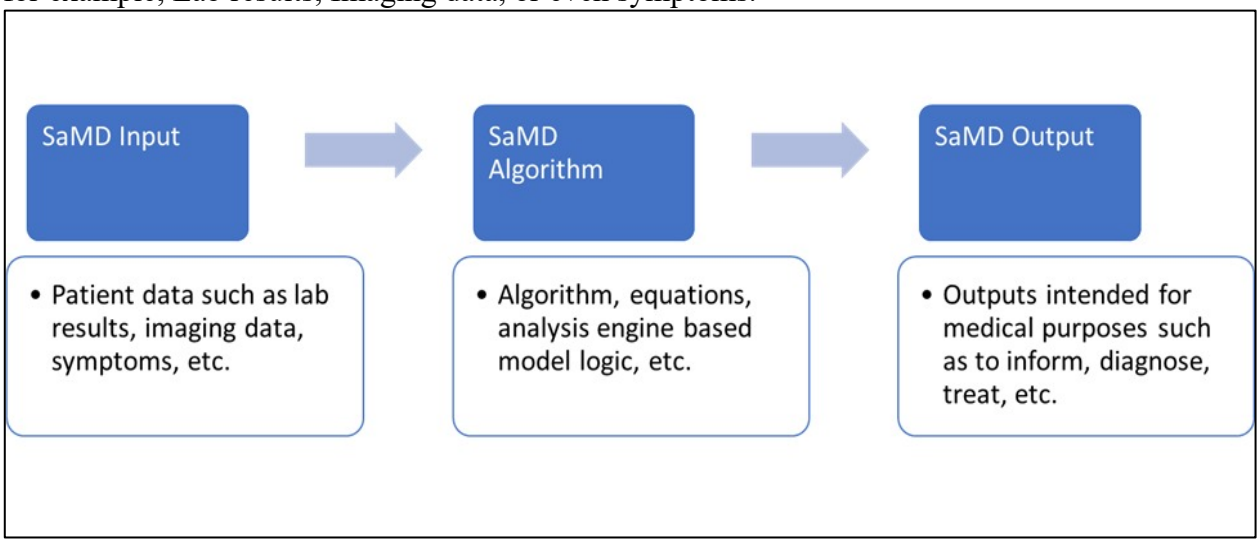
1.2.4. Digital therapeutics

It helps in the treatment of small or life-threatening diseases as well as chronic diseases by enrolling on any smart medical device.

1.3. SaMD workflow

SaMD medical devices may include in-vitro diagnostic devices. A device is not considered a SaMD if its intended application is to drive a hardware medical device. Furthermore, it can be paired with hardware or any other SaMD software and can run on general or non-medical-purpose computing platforms.

A SaMD software creates an output using an algorithm that follows the input data, which can be a patient's data, for example, Lab results, Imaging data, or even symptoms.



2. SaMD AND ITS ALGORITHMS

SaMD medical devices work on different kinds of algorithms which are discussed below.

2.1. LOCKED AND ADAPTIVE ALGORITHM

Think about two different hypothetical AI-established tools in the healthcare industry. Hypothetical tool A and Hypothetical tool B. Tool A have been strictly equipped with existing tools that will give strong outcomes on what is known in those data inputs.

While, Tool B, is more likely trained to analyse data from real life around the globe to get new insights and improve on its suggestions.

Potentially, the later type of AI which is dependent on an "adaptive" algorithm shows more capability, especially in cases of poorly understood conditions. Up to this point, the tool A algorithm has been approved by regulatory bodies like the FDA, but in 2019 FDA issued a white paper to declare a regulatory framework for adaptive algorithms and were open for feedback from stakeholders.

2.1.1. LOCKED ALGORITHMS:

In the past regulatory authorities have approved locked algorithms. According to FDA locked algorithms can be defined as an algorithm that gives the same result every time the same input is added and does not change. The Medical Futurist Institute achieved the first open-access online database of these FDA-approved algorithms.

For example, KardiaAI in AliveCor's personal is an ECG monitor that alerts the users if any suspicious reading is monitored. Likewise, the IDx-DR can screen diabetic retinopathy from a retinal camera.

These algorithms work on the static approach of locked algorithms. If the healthcare system wants AI to be more accurate, they will need to train AI to fetch new data sets.

2.1.2. ADAPTIVE ALGORITHMS:

FDA defines an adaptive algorithm as one that changes its behaviour using a defined learning process. The changes are added such that the output can be different for a given set of inputs.

The potential that the adaptive algorithm shows is that it learns continuously and self-improves without any input from others. It would be able to learn from real-world experiences.

Researchers developed an algorithm to detect diabetic retinopathy with almost 90% accuracy. However, in reality, the accuracy was low due to issues faced in the quality of the images. In the case of AI, it could adapt to these changes to deliver results by training on types of image quality, even it wasn't initially trained to do so.

Such types of AI have the potential for the next step in the healthcare industry. And a future can be visioned by the FDA for adaptive algorithms to make their way into the market.

2.2. UTAUT Model

The unified theory of acceptance and use of technology (UTAUT) has been developed from the classic technology acceptance model (TAM) which was proposed by Davis (1989) followed by the extended TAM (ETAM) and finally the UTAUT model by Venkatesh et al. He compared and analysed 8 distinct models that were related to behavioural intention and embedded into the UTAUT, this consists of 4 different variables that influence the usage of new technology.

2.2.1. Performance expectancy

Performance expectancy can be defined as the level to which a person believes that using an innovative medical device help them to achieve their work-related goals.

2.2.2. Effort expectancy

Effort expectancy can be defined as the extent to which an individual perceives or understands when using a new medical device.

2.2.3. Facilitating conditions

Facilitating conditions can be defined as an individual belief that the organizational and technical infrastructure pertains to support the use of innovative medical devices.

2.2.4. Social influence

Social influence can be defined as the effect of usage of the devices by the people of their surrounding vicinity over their beliefs regarding the device's usage.

The application of UTAUT has been an important aspect in examining the usage of new systems by healthcare professionals, Holden and Karsh studied how UTAUT can be applied to understand the acceptance of electronic health records.

UTAUT has also been used to study the acceptance of advanced digital tools in the healthcare system, for example, Telemedicine and AI-driven diagnostics. The continued use of UTAUT in medical technology depicts its relevance in understanding the area of technology adoption in healthcare. It provides a level of understanding for healthcare organizations to support in transitioning to technologically advanced systems.

3. ETHICAL CONCERNS RELATED TO SaMD MEDICAL DEVICE:

The use of AI-based SaMD medical devices has a huge ability to transform healthcare delivery for good but there exist ethical concerns too. The five major components of ethics include:

- Patient autonomy
- Non-malfeasance
- Distributive justice
- Utility
- Beneficence

These can also include population selection bias in training and validation cohorts. Other examples can include issues related to privacy and property of data, patient autonomy, and freedom.

3.1. PATIENT AUTONOMY:

It is a fundamental principle in medicine that emphasizes the rights of the patient to make their own decision of health. It also tells that individuals have the right to decide what happens to their bodies and to take part in

their treatment. Healthcare professionals must obtain the patient's consent and the patient should also be aware of all the risks and benefits before starting the treatment.

3.2. NON- MALFEASANCE:

It is an ethic that states that a physician must not harm the patient. It also tells us that a doctor must consider all the benefits and weigh them against the potential risks and burdens on the patient.

3.3. DISTRIBUTIVE JUSTICE:

Distributive justice is an integral ethical principle. The main principle of distributive justice says that health services are available to a person by his/her needs and also within the context of resource availability.

3.4. UTILITY:

It can be defined as the theory of morality that advocates actions that favour happiness or pleasure and opposes actions that cause unhappiness. When directed toward the healthcare system it would aim for the betterment of society.

3.5. BENEFICENCE:

It is a medical ethics that states to make a decision that is in the best interest of the patient.

Therapeutic goods generally have two regulations that are sometimes at odds with each other. Regulations try to safeguard public health and at the same time allow innovations to reach the market as quickly and reasonably as possible. How a regulation achieves both aims is when manufacturers present proof of a product's safety and effectiveness. Firstly, this protects customers from using products that are unsafe or won't be beneficial. Secondly, it means that commercial success should be based on research.
Such a side of regulation deals with difficult situations about the evidence it will require. To answer these questions scientific input as well as ethical decisions are required such as the level of risks involved and which two regulations should outweigh the other.

4. REGULATIONS ON SaMD:

4.1. USA:

In the USA FDA is responsible for regulatory approval. The federal agency supervises and regulates items for example food, pharmaceutical drugs, and cosmetics. They also regulate medical devices and veterinary products. FDA works by proposing, reviewing, modifying, and revising which are then placed in the Code of Federal Regulations (CFR), Title 21, Parts 800-1299. FDA is also the Centre for device and Radiological Health (CDRH) which ensures that there is minimal exposure from radiation-emitting medical devices.

- FDA discussion paper:

In April 2019, a discussion paper was published by the FDA on AI-ML-based SaMD. As a part of the proposed framework, the FDA put forward a pre-determined change control plan in pre-market submissions which is composed of SaMD pre-specification and algorithm change protocols.
A total product life cycle (TPLC) application proposed by the FDA for a regulatory approach to AI-ML-based SaMD. TPLC allows assessment of the product from the pre-marketing stage to the post-marketing surveillance stage to ensure quality, safety and effectiveness.
TPLC approach is based on the following principles:

– Quality systems and good ML practices (GMPL)
– Initial pre-market assurance of safety and effectiveness
– Approach for modifications after initial review with an established SPS and ACP
– Transparency and real-world performance (RWP) monitoring AI-ML-based SaMD

4.2. Europe:

Europe has a separate set of regulations for medical devices, Medical device regulations (MDR). The European Commission in association with the Medical Device Coordination Group (MDCG) is responsible

for developing regulations for SaMD. The working groups oversee the issues from notified bodies, clinical investigations, post-marketing surveillance, international issues, implementing the EUDAMED database, and also implementing IVD and Annex-4 products.

MDCG guidance documents name SaMD as medical device software (MDSW) especially in European countries. MDSW can be distinguished as low risk (Class-Ia), medium risk (Class-IIa), medium-high risk (Class-IIb), or high risk (Class-IIIa). MDSW can be used alone or in classification (Article 2(1), EU MDR 2017/745).
MDCG guidelines dictate the requirements for a product to be classified as in MDSW under EU MDR. There are mainly two ways in which an MDSW product can be marketed-

1) As a medical device in its own right
2) Or as an important component of any medical device

The former needs an in-depth regulatory process that includes a validation process to determine whether the device needs EUMDR requirements. However, that requirement is not applied in the latter, as a result, an important component of the medical device can be marketed based on the medical device only and not on its regulatory process.
MDCG is in the main body for formulating the harmonized regulatory standards for all EU member states regarding AI.

4.3. JAPAN:

REGULATORY AUTHORITIES IN JAPAN:

MHLW

- Final Authorization of applications
- Publishing Guidelines
- Supervising PMDA Activities

PMDA

- Scientific Review
- Consultation on Clinical Trials etc.

MHLW- Ministry of Health, Labour and Welfare
PMDA- Pharmaceuticals and Medical Devices Agencies

GTHF Classification		Classification in Japan			
Class	**Risk Level**	**Class**	**# of JMDN****	**Category**	**Pre-market regulation**
A	**Low** Surgical retractors/ Tongues depressors	I	1,225	General MDs	Self declaration***
B	**Low to moderate** Hypodermic needles/ Suction equipment	II	2,027	Controlled MDs + Designated controlled MDs	Third party certification (Review by RCB*) (Designated controlled MDs and Designated specially controlled MDs)
C	**Moderate to high** Lung ventilator/bone Fixation plate	III	826	Specially controlled MDs + Designated specially controlled MDs	Ministerial Approval (Review by PMDA) (Controlled MDs and specially controlled MDs)
D	**High** Heart valves/ Implantable defibrillator	IV	375		

4.4. INDIA:

In September 2021, CDSCO declared official guidelines on the various classifications of SaMDs. It is classified into 4 risk categories such as low-risk (Class A), low-moderate risk (Class B), moderate risk (Class C) and high-risk (Class D) devices

- **Licensing requirements:**

SaMDs need to be registered according to the Medical Device Registration Pathway. Medical devices can be sold in three ways they are (1) by the Distributor (2) by Independent Authorized Agent and (3) by the Indian subsidiary. This means that you can sell only if you have an Indian company holding your license.

- **ADDITIONAL REGULATIONS:**

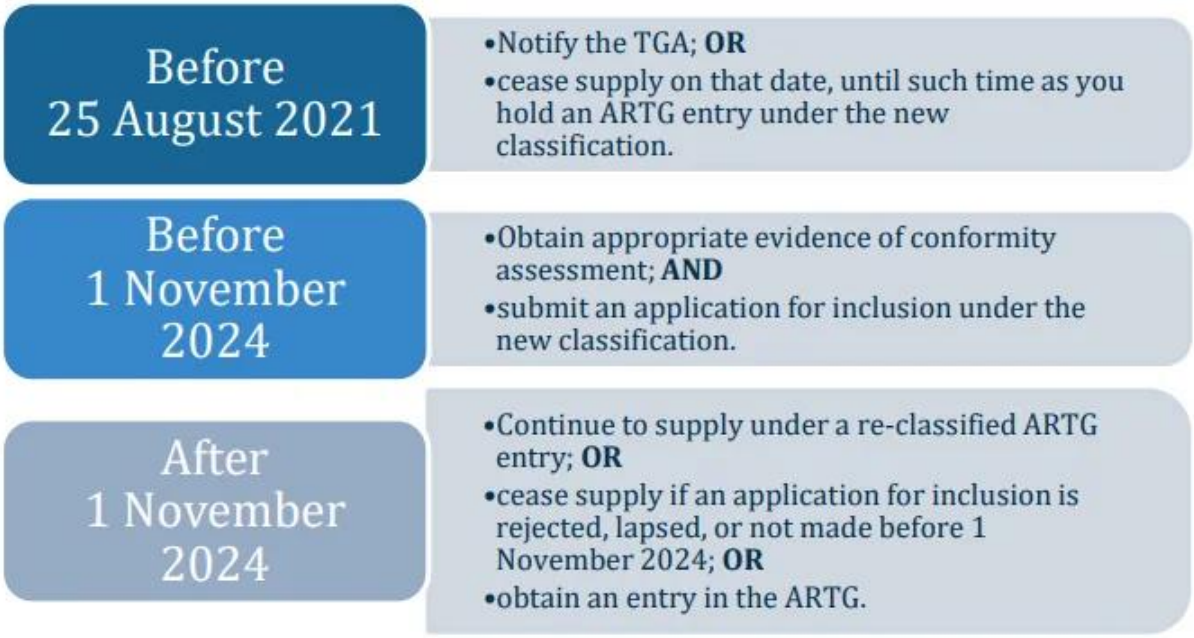
A Samd to be marketed in India must follow all the following regulations:

A. Gazette S.O. 648(E) from February 11, 2020
B. Medical Device Rules from 2017
C. ISO 13485:2016 - Quality Management Systems
D. ISO 14971:2019 - Implementation of Risk Management to Medical Devices

SaMDs also need to comply with global standards which are:

A. IEC 62304 - This defines the lifecycle of a SaMD
B. IEC 62366-1 - This talks about man-machine interface ergonomics
C. IEC 60601-1 - This refers to the software which is embedded in the hardware of a Medical Device
D. IEC 82304-1 - This applied to standalone SaMD's
E. IEC 81001-5-1 - This talks about Cybersecurity

4.5. AUSTRALIA:



5. COMPARATIVE ANALYSIS OF REGULATIONS:

As discussed about the regulations on SaMD in different countries a similarity can be seen in all the countries which is the classification of the medical devices based on their risk. The categories given to the SaMD vary from country to country. The regulations of each country are very different because of different regulatory authorities and the different functions they perform.

In the USA FDA is the regulatory authority, they also classify their medical devices into various categories, The FDA works on a TPLC approach ensuring the safety and effectiveness of the SaMD.

In Europe, MDCG is responsible for developing regulations for SaMD, they also have a distinct set of regulations known as medical device regulations (MDR). MDCG forms regulations for marketing SaMD for the safety of patients.

Similarly, different countries have different regulatory authorities and different regulations to comply with which are to be followed by the applicant to ensure the safety of the device.

Aspect	India	USA	Europe	Japan	Australia
Regulatory Body	Central Drugs Standard Control Organization (CDSCO)	Food and Drug Administration (FDA)	European Union (EU) - Medical Device Regulation (MDR)	Pharmaceuticals and Medical Devices Agency (PMDA)	Therapeutic Goods Administration (TGA)
Regulatory Framework	Draft regulations under Medical Devices Rules, 2017	Regulatory framework released in 2019	Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR)	Guidelines established by PMDA	Guidelines for software as a medical device (SaMD)
Emphasis on Transparency	Evolving	Emphasized, requiring detailed documentation on algorithms	Emphasized, requiring transparency in algorithm usage	Emphasized, guidelines for transparency and accountability	Emphasized, guidelines for traceability and transparency
Speed of Approval	Variable	Lengthy process, rigorous evaluation criteria	Variable, but typically more time-consuming	Efficient process, quicker approvals	Efficient process, relatively quicker approvals
Adoption of International Standards	Adopted international standards for quality management	Adopted international standards for quality and risk management	Adopted international standards for quality and risk management	Adopted international standards for quality and risk management	Adopted international standards for quality and risk management

6. DIGITAL TWIN: AN SaMD SOFTWARE

The increase in manufacturing complexity in a more demanding market is collecting momentum for the integration of the physical and digital worlds. Likewise, humans' increasing practical needs for industrial products are questioning the digital model's ability to interact with physical objects. The digital twin was considered in this context and has ignited a far-reaching industry revolution.

A digital twin is a concept that creates an "in-silico" model, a computerized dummy of a patient and their physiology that can be used in a clinical or research setting. In other words, it is an exact duplicate of a patient in a primary clinical state. They are designed using real-life patient data and a concept-based understanding to stimulate the model based on real-life scenarios without putting patients' health at risk. They also use machine learning algorithms to operate large quantities of sensor data and identify data patterns. AI/ML provides data insights into performance optimization, maintenance, emissions outputs, and efficiencies.

A potent digital twin model needs to be built from multiple digital twin modelling aspects. Digital twin modelling can be built from the six aspects of model construction, model assembly, model fusion, model verification, model modification, and model management.

There are mainly three important parts to the digital twin:

1. Model of the object
2. Evolving set of data relating to the object

3. Means of dynamically updating or adjusting the model by the data.

The model that is used in Digital Twin need not be necessarily a data-driven model, but at the same time it should give outputs that are directly equivalent to a measured quantity, and also the model will take other measured quantities as boundary conditions, loads, or material properties.
The utilization of other data also means that it is an important aspect of the digital twin approach and it also provides an accurate description of objects that change over time.
One of the important aspects of the digital twin is that it should be associated with an object that exists in the real world: a digital twin without a physical twin is a model. Biological identical twins are created at the same time and continue to develop and grow at the same time. this concept of the resemblance of two things throughout development and evolution is an integral feature of the true digital twin, and for this analogy to be possible, the physical twin must also exist.
The result of the requirement for the physical object to exist is mainly for the design of a digital twin, and it is necessary when the prototype stage has been achieved. At the prototype stage, the common step is to test the prototype and update the model based on the output.

6.1. NEED OF A DIGITAL TWIN:

A digital twin is needed when an object is evolving, thus making the initial model of the object invalid. One main reason this concept is very important in manufacturing is that it allows for the development of individual models of individual objects within one framework.

The concept of digital twins offers various benefits in medicine. The ability to alter the drug characteristics, implant, and prosthetic geometries, and plan the treatments for the needs of individual patients will lead to more efficient treatment with fewer side effects and improved health outcomes. Examples include changing drug dosage by patient response also to monitor damage and wear of prosthetics.

6.2. KEY CONCEPTS REGARDING DIGITAL TWIN:

A digital twin model works on various aspects which are as follows:

6.2.1. BIDIRECTIONAL MAPPING:

Digital twins are not just a unidirectional map, it is a digital representation, or stimulation model of a real-world human being in the digital world. Digital twins can constructively transform into virtual representations of their real-world twins, they can be affected by the physical body they represent. In a digital thread, it can create a channel over time, for example, from a person's birth to death.

6.2.2. DIGITAL TWIN TYPES:

Digital twins type includes the human body, a single organ, a cell, a particular disease, or a virus. Healthcare organizations can have two digital twins at the same time of the same physical organism to better monitor their function.

6.2.3. Identical copies:

Identical copies of digital twins can help a patient to choose from various treatments or which treatment can be more useful.

6.3. REGULATORY REQUIREMENTS OF DIGITAL TWIN:

The main regulatory requirement for digital twins starts with the Atomic Energy Act (AEA) as amended, which an applicant must comply with. AEA is the primary regulatory requirement which were implemented by NRC.
Title 10 of the CFR and commission orders are the mandatory rules to be followed by NRC staff to implement the law
According to I&C if a DT provides any specific system, then it must comply with all the necessary requirements of that system.

7. CONCLUSION:

SaMD has a great ability to improve health and health care at individual and system levels. To ensure patient safety and also the effectiveness of the SaMD all the regulatory standards shall be complied with. Adaptive algorithms will increase the precision of the decision of an SaMD therefore it may be perfect to adapt that

algorithm in as many devices as possible. The main challenge of SaMD lies in the misalignment between the different regulatory authorities. This issue can be solved by formulating a common framework that allows manufacturers to focus on innovation and also patient safety . Digital Twin has been rapidly advancing from concept to application in recent years. The main challenge with digital twins lies in the privacy of the patient, which can be overcome by increasing the cyber security of the software.

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