White Paper

ClinChoice
The Standard of Excellence

SOFTWARE MEDICAL DEVICES

An Overview of Regulations, and Challenges

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1. Introduction

In the age of rapidly advancing technological innovation, we're seeing more and more modern active medical devices that in some way interact with software. As digital technology has advanced in all areas, dependency on software has also increased exponentially in the field of healthcare. The dependency has primarily grown due to the ease of use and accessibility of software through a wide range of platforms. For example, all the relevant data can be stored on a computing platform through cloud computing and made accessible to users, enabling the use of a tremendous amount of computing power for making real-time decisions in disease modeling. In addition, the high-speed network (5G+) can enable real-time data of video and audio quality for patient data analysis, telemedicine, medical, and surgical intervention.

There are three main types of software used in the medical field **(Figure 1):**

- Software in a medical device (SiMD), that is integrated into medical devices such as software that controls a magnetic resonance imaging (MRI) machine or software that enables users to manage insulin pumps based on blood glucose levels.
- Software as a medical device (SaMD), is independent software that functions as a standalone medical product. For example, heart rate monitors, BMI calculators, software that enables the visualization of MRI or other medical imaging on mobile, or software that suggests treatment.
- Software that is used in healthcare but not considered medical devices such as Digital Health Records, Medical Information Systems, 3D printing, etc.

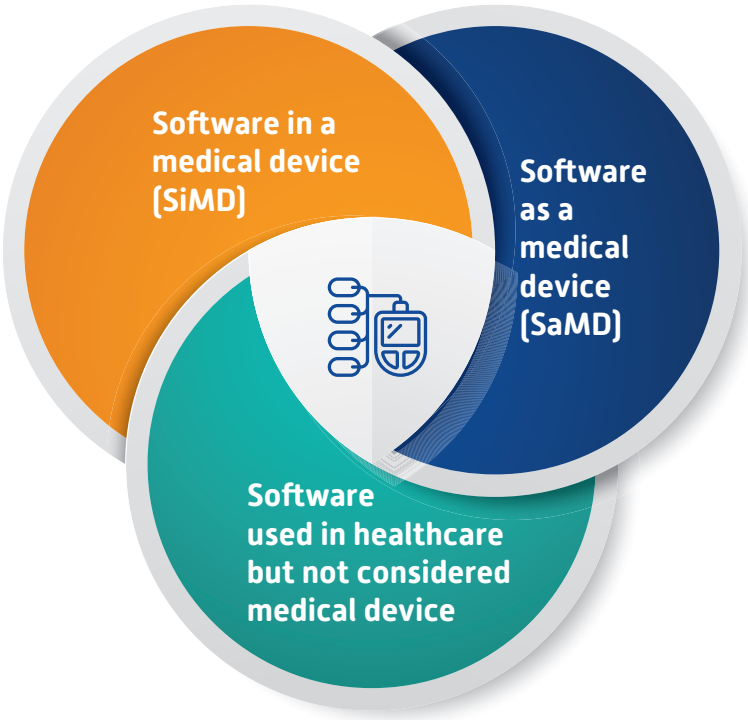

Figure 1: Software in Medical Field

The software medical device brings new opportunities and challenges for both device companies and regulators. To support innovation while maintaining patient safety, different regulatory paradigms are being examined in this area.

More recently, artificial intelligence (AI) approaches are being incorporated into software medical devices, which may be described as artificial intelligence as a medical device (AIaMD).[1] The AI component of AIaMD may be variable in complexity and significance. Broadly AI may be defined as 'the science of developing computer systems which can perform the tasks through machine learning (ML), which normally requires human intelligence.'

Learning more about what software medical device is and how it works can benefit an organization looking to integrate their own device with software. It may also help manufacturers understand if their software falls under the medical device category. This paper is intended to provide insights into software medical devices focusing mainly on guidelines/regulations in the United States (US) and European Union (EU). It also highlights the clinical evaluation process and the current challenges faced by manufacturers in this industry.

2. Overview of Software Medical Devices

Software medical devices are software or applications that are used to treat, diagnose, cure, mitigate, or prevent diseases. They are typically used with computing platforms connected to virtual networks or other general-purpose hardware. Standalone software medical devices are a particularly emerging category of healthcare software resources. In the US, the term used for such devices is software as medical device (SaMD) whereas, in Europe, the term "medical device software" (MDSW) is used.

The International Medical Device Regulators Forum (IMDRF) defines SaMD as "*software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.*" [2.3]

A few examples for SaMD include:[4.5]

- Software that enables a mobile device to view diagnostic images from an MRI, ultrasound, or X-ray.
- Image-processing software that aids in the detection of breast cancer.
- Software that captures real-time patient data and uses it to suggest treatment plans.

The European Commission's Medical Device Coordination Group (MDCG 2019-11) defines MDSW as "*software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a 'medical device' in the Medical Device Regulations (MDR) or In-Vitro Diagnostic Regulations (IVDR), regardless of whether the software is independent or driving or influencing the use of a device.*" A MDSW is classified as an In-Vitro Diagnostic (IVD) medical device if its intended use is related to the testing of human samples such as software used for genetic testing to predict the risk of a medical condition and software used for the calculation of anticoagulant dosage based on inputs from test results provided by IVD instruments and other patient data.[6]

As it is clear from the two definitions, SaMD and MDSW are not just the different terms used for software medical devices in different regulatory jurisdictions but are also defined differently. If a software device achieves one or more medical purposes independently, then it falls under both SaMD and MDSW categories; however (unlike SaMD), MDSW also includes accessory software that is necessary for a medical device to achieve its medical purpose. For example, an insulin dose calculator falls under the MDSW category for driving the infusion pump but cannot be considered SaMD.

History

The software has evolved in the last few decades from being a component of medical innovation to being at the heart of new product launches (refer to **Figure 2**).[5]

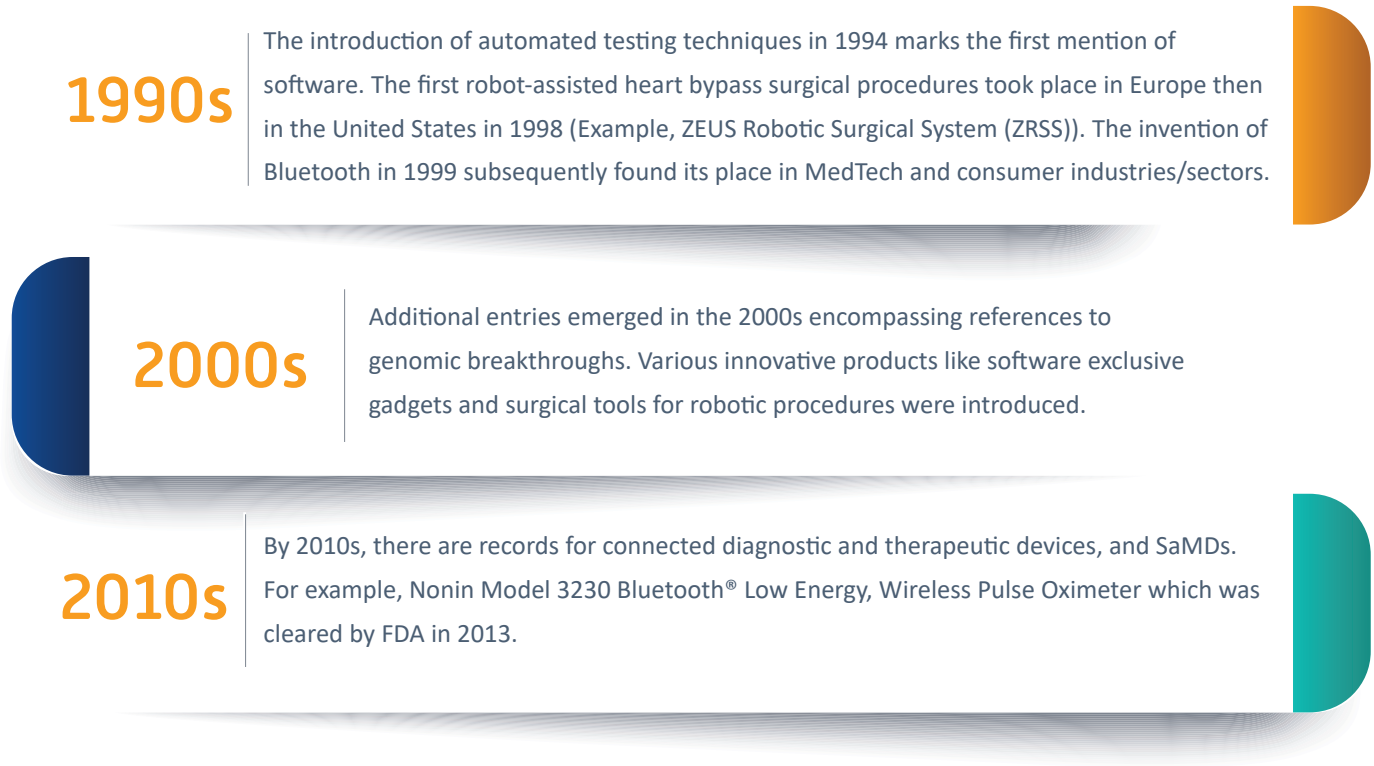

Figure 2: Evolution of Software Medical Devices

Though software's have been used in the medical field for more than three decades now, the ever-changing regulations create significant confusion regarding the classification and regulatory requirements.

3. Classification, Regulatory Requirements, and Guidelines

Classification:

A risk-based approach has been the main criteria for determining the regulatory framework in software (medical device) development and distribution. Software medical devices generally tend to fall in lower risk classes unless errors, in the contexts of treatment or diagnosis, which could lead to a serious deterioration in a patient's health. They follow a similar classification pattern that is applicable to general medical devices. In the US, the manufacturer classifies SaMD by determining applicable product codes and thereby matching device class. If no code appears to fit, a request for information to the FDA is submitted. As per FDA classification, Class I or Class II devices require either a 510(k) or De Novo submission based on the availability of a predicate device and Class III requires a Premarket Approval (PMA). In contrast, European classification is more complex with Class I, IIa, IIb, and III under EU MDR and Class A, B, C, and D under EU IVDR.[7,8]

The manufacturers of software medical devices should consider all the regulatory requirements to fit into the required regulatory framework for introducing their devices and maintaining them on the market throughout the lifecycle. An FDA guidance document "Content of Premarket Submission for Device

Software Functions" and an EU MDCG guidance document "MDCG 2019-11 - Guidance on Qualification and Classification of Software in Regulation (EU) 2017/245 – MDR and Regulation (EU) 2017/746 – IVDR" have been the base reference for the current regulatory requirements for SaMD and MDSW, respectively.

Regulatory Framework under FDA:

To suit the rapid advancements in software and digital solutions, FDA established the Software Precertification Pilot Program in 2017 and published a report on their key findings in 2022 that focused on total product lifecycle approaches. The rapidly evolving technologies in the software medical device landscape could benefit from a new regulatory paradigm based on the observations from the pilot report which may pave the way for new legislative change.[9]

Except for simple minimal-risk SaMDs, manufacturers are required to submit a 510(k) notification/De Novo request/PMA application for marketing approval in the US based on the risk level of the SaMD.

A 510(k) application must demonstrate that the device to be marketed is as safe and effective as a medical device that is legally marketed and is substantially equivalent. Medical device manufacturers (Class I and Class II) are required to submit a 510(k) application, when their devices are not exempted from 510(k) requirements of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), or when there is a significant impact on the safety and effectiveness of a legally marketed existing device due to any changes or modifications in the design, components, method of manufacture, labeling or intended use.[10]

The recommended documentation for a premarket submission of a device software function is based on the device's risk to the patients, the user of the device, and those in the environment of use. The FDA employs a risk-based approach (risks associated with the device's software functions and intended use) to determine documentation level (Basic or Enhanced). For instance, devices used to determine blood cell separation, blood donor and recipient compatibility, and blood establishment computer software typically require Enhanced Documentation due to their specific risks. Similarly, combination products (drug/device or biologic/device or drug/device/biologic) and Class III devices require Enhanced Documentation, although sponsors may provide a detailed rationale if Basic Documentation is deemed sufficient. During documentation level determination, sponsors should bear the responsibility of thoroughly assessing all known/foreseeable software hazards and hazardous situations associated with the device, including the possibility of misuse and inadequate cybersecurity. Some examples of devices with software functions categorized under these two documentations are provided in **Figure 3**.[11]

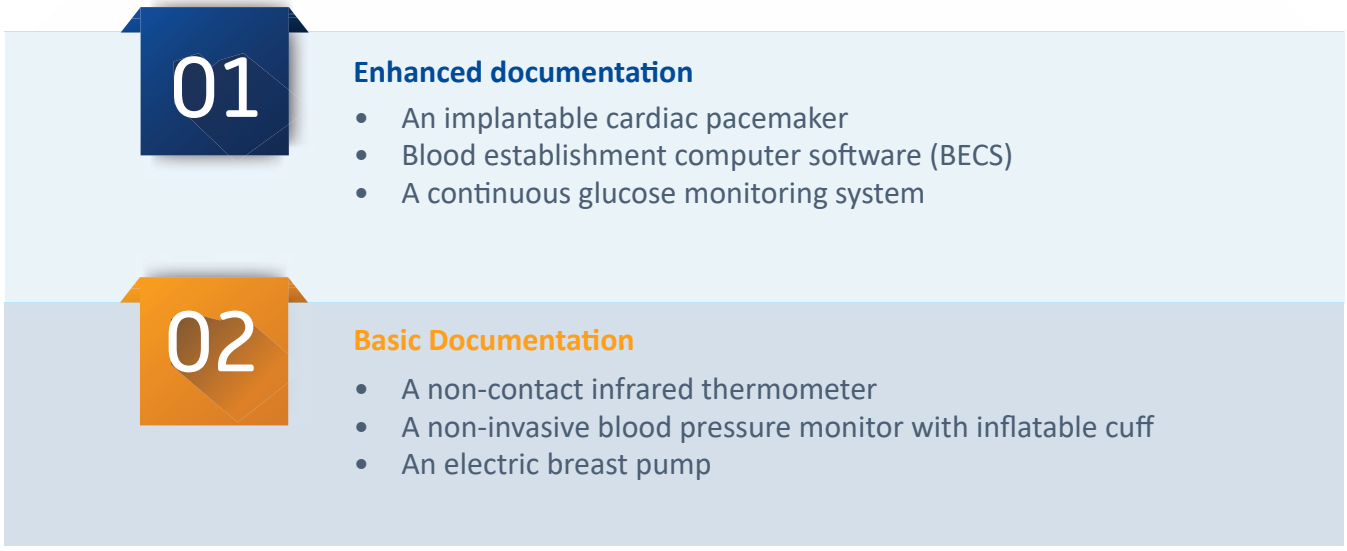

Figure 3: Documentation Level

For novel devices with no legally marketed predicate device/equivalent device, a De Novo request can be submitted to obtain marketing authorization for low/moderate risk devices. The final rule (effective since 03 January 2022) issued by the FDA under the FD&C Act establishes the requirements for the SaMD De Novo classification process. These devices that fall into either Class I or Class II through De Novo classification request may be used as a predicate device (or marketed device) in the future for filing of application for similar devices through a less cumbersome premarket [510(k)] submission process.[12] For example, Apple Watch electrocardiogram (ECG) App was classified as Class II by FDA a few years back through a De Novo application process.[13] This was followed by Google's Fitbit irregular rhythm app which was cleared as a Class II device based on the premarket [510(k)] notification process.

The premarket approval application is a rigid and rigorous type of device marketing application by FDA. The process mainly reviews the scientific and regulatory aspects of the device to evaluate the safety and efficacy of Class III medical devices. As these devices are associated with high risk, general and special controls are insufficient to assure safety and efficacy and hence require a PMA application.[14]

Experts argue that the above-mentioned traditional regulatory pathway (Premarket approval pathway) or approval of medical devices is not suitable for the modern SaMDs which may also use AI. Hence, FDA is planning to change its approach towards advanced SaMDs. In the discussion paper published in 2021, "Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan" the FDA laid the foundation for a new approach for regulation of modern SaMDs/AIaMDs. Based on this approach, the FDA may establish a regulatory framework in which a "predetermined change control plan" (types of anticipated modifications and the associated methodologies to implement the modifications in a controlled manner) would be required with premarket submissions for AIaMDs.[15]

There are many simple minimal-risk SaMDs for which the FDA intends to exercise enforcement discretion. Examples of such SaMDs include devices that help patients in self-managing their diseases or devices that automate simple tasks of surgeons and nurses. FDA has provided a list of such devices at Examples of Software Functions for Which the FDA Will Exercise Enforcement Discretion | FDA.

Regulatory Framework under EU:[5]

For placing MDSW in the European market, the manufacturers must ensure all the regulatory requirements and conformity assessment have been fulfilled as per MDR/IVDR. Technical documentation needs to be filed for every device irrespective of the device classification. The Class I devices are self-certified without the involvement of the notified body and Class II and Class III devices require notified body approval for Conformité Européenne (CE) marking.

In the EU MDR, MDSW is majorly classified through Rule 11, and 15. As Rule 15 of MDR covers those devices which are used for contraception/prevention of transmission of sexually transmitted diseases, the software devices that assist in these processes are classified as IIb. Other rules for active medical devices and some special rules such as Rule 12, 13, and 22 may also be used to classify software medical devices. However, currently, there are no such devices that fall under these categories as per our knowledge.

With the recent changes in regulations from MDD to MDR and the addition of Rule 11 in Annex VIII of the MDR, a few Class I devices are upclassified as Class III devices (e.g., a stand-alone software application for automated mobile testing system software). As Rule 11 is based on severity, preventive software or monitoring software which is simple and low-risk software used for diagnostic purposes are now classified as Class I.[5] The implication of up-classification to Class III is that the MDSWs that were safely on the EU market with MDD or Active Implantable Medical Devices Directive (AIMDD) certificate will have to

comply to all the MDR regulatory requirements for Class III devices which may include performing clinical investigations and soliciting the opinion of an expert panel.

An EU regulatory approach for MDSW differs significantly from an FDA approach. As discussed above in **Section 2**, MDSW includes not only a standalone software device but also software that drives/influences the actions of another medical device. This impacts the risk classification of MDSW, which in most cases takes a higher classification than warranted.

Table 1 below outlines the standards and guidelines applicable to SaMD/MDSW. [16,17,18,19,20]

Table 1: Standards and Guidelines Applicable to SaMD/MDSW

Standards	**General Standards**
	ISO 13485:2016 Quality Management System for design and manufacture of medical devices
	ISO 14971:2019 Risk Management for medical devices
	ISO 14155:2020: Clinical investigation of medical devices for human subjects - Good clinical practice
	Software Specific Standards
	IEC 62304:2006/Amd 1: 2015: Medical device software – Software life-cycle processes – Amendment 1
	IEC 60601-1:2005 Section 14: Programmable electrical medical systems (PEMS) in medical devices
	IEC 62366-1:2020 Usability in medical devices
	IEC 81001-5-1: Cyber Security
	IEC 80002-1:2009: Medical device software - Part 1: Guidance on the application of ISO 14971 to medical device software
	ISO 82304-1:2016: Health software – Part 1: General requirements for product safety
Guidelines-EU	IMDRF/SaMD WG/N41FINAL:2017
	MDCG 2018-5 UDI Assignment to Medical Device Software
	MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745-MDR and Regulation (EU) 2017/746 – IVDR
	MDCG 2019-16 Guidance on Cybersecurity for medical devices
	MDCG 2020-1 Guidance on Clinical Evaluation (MDR)/Performance Evaluation (IVDR) of Medical Device Software

Guidelines-FDA	Software as a Medical Device (SAMD): Clinical Evaluation Guidance for Industry and Food and Drug Administration Staff DECEMBER 2017
	Artificial Intelligence and Machine Learning in Software as a Medical Device
	Content of Premarket Submissions for Device Software Functions, Guidance for Industry and Food and Drug Administration Staff, JUNE 2023

Note: The standards/guidelines in effect at the time of this publication

4. Clinical Evaluation Process

'Clinical evaluation of a SaMD/MDSW', is defined as a "*set of ongoing activities conducted in the assessment and analysis of a device's clinical safety and performance as intended by the manufacturer. It is a systematic, planned, transparent, iterative, and continuous process to generate clinical evidence verifying the clinical association and the performance metrics of the device.*" The device manufacturer is expected to implement ongoing lifecycle processes to thoroughly evaluate the safety and performance of a product before and after its launch.[18, 21, 22, 23]

As per MDCG-2020-1, software, that qualifies as a Medical Device or an IVD, is subject to the same general clinical evaluation (MDR)/performance evaluation (IVDR) principles or legal requirements that are laid down in the applicable guidelines and regulatory documents, as other Medical Devices/IVDs.[22]

Why is Clinical Evaluation Required for SaMD/MDSW?

Healthcare decisions increasingly rely on information provided by the output of devices and these decisions can impact clinical outcomes and patient care. In order to demonstrate assurance of safety and performance, global regulators expect that performance measures for a software medical device have a scientific level of rigor that is commensurate with the risk and impact of the device.[18, 20]

Identification of Data for Clinical Evaluation

Clinical evaluation includes demonstration and analysis of device equivalence or device-specific data from non-clinical and clinical studies or a combination of both. For software medical devices, manufacturers can also use technical data and state-of-the-art evidence. The challenge for software medical device manufacturers is to find starting points for complying with basic performance and safety requirements.

The three key components required for compiling clinical evidence for SaMD/MDSW* include:

- Valid Clinical Association (MDR)/Scientific Validity (IVDR)
- Technical/Analytical Performance Validation
- Clinical Performance Validation

**Technical/analytical or clinical performance validation is collectively referred to as 'Product Performance'* or 'Verification & Validation (V & V) Phase of Software Lifecycle'.[18,20,22]

1) Valid Clinical Association/Scientific Validity

Valid clinical association/scientific validity is referred to as the extent to which the device output (e.g., concept, conclusion, measurements) based on the inputs and algorithms selected, is associated with the targeted physiological state or clinical condition. This association should be well-founded or clinically accepted by the broad medical community and/or described in scientific (peer-reviewed) literature. However, this association is not always readily established. So, the 'clinical performance' serves as an additional input to the valid clinical association/scientific validity for the specific intended purpose.

Figure 4 represents the steps to conduct a valid clinical association.[18,20,22,24]

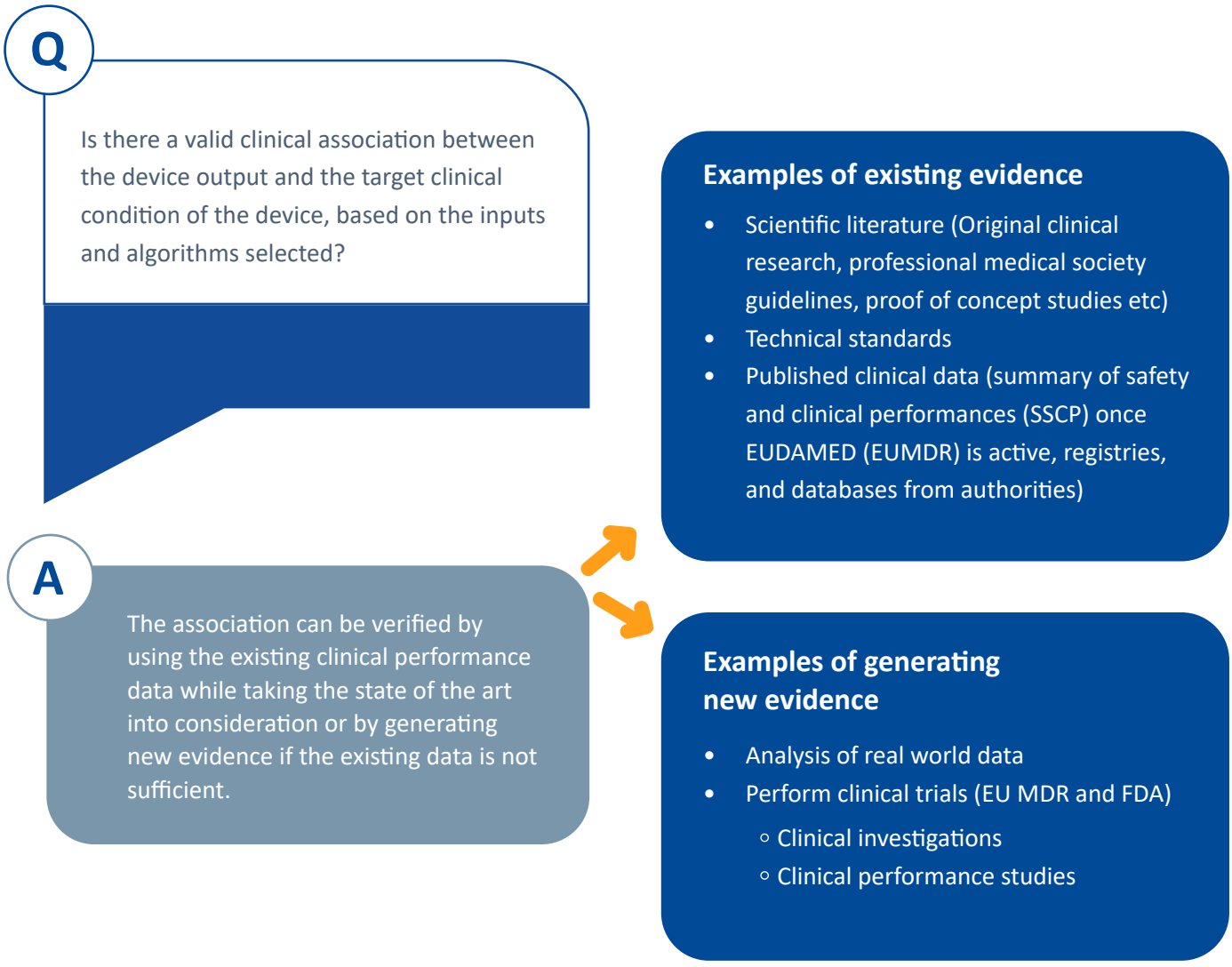

Figure 4: Valid Clinical Association/Scientific Validity

2) Technical/Analytical Performance Validation

Validation of the technical/analytical performance is the demonstration of the device's ability to generate the intended technical output accurately, reliably, and precisely from the input data. The manufacturer should verify that the device meets the intended purpose in real-world usage. **Figure 5** represents the steps to conduct a technical or analytical validation.[18,20,22,23,25]

Q: Does the device meet technical requirements?

A: Evidence can be generated through verification and validation activities (e.g., unit level integration, system testing) as part of the quality management system or as part of good software engineering practices. Identification of gaps during the validation of the technical / analytical performance could require the generation of new evidence through the use of curated databases and registries, reference databases, or by use of previously collected patient data.

Figure 5: Technical/Analytical Validation

3) Clinical Performance Validation

Clinical performance validation measures the ability of a device to yield a measurable, positive patient-related clinical output associated with the intended purpose of the device in the target healthcare situation or condition. It can also be viewed as the relationship between the verification and validation results of the device algorithm and the clinical conditions of interest.[18,20,22,23] **Figure 6** demonstrates the performance verification and validation characteristics.[22,24]

Verification – confirmation through provision of objective evidence that specified requirements have been fulfilled.

Validation – confirmation through provision of objective evidence that the requirements for a specific intended use of application have been fulfilled.

Examples: Analytical sensitivity, limit of detection, limit of quantification, analytical specificity, availability, confidentiality, integrity, reliability, accuracy, linearity, cut-off value(s), measuring interval (range), generalizability, expected data rate of quality, absence of inacceptable cyber security vulnerabilities, human factors.

Figure 6: Performance Verification and Validation

Manufacturers should evaluate and determine clinical validity during the development of a device in the pre-market and post-market stages. A justification should be stated in the technical documentation if no validation is performed at each change made during its lifecycle. **Figure 7** represents the steps to conduct a clinical validation.[18,20,22,23]

Does the device generate clinically relevant outputs?

Evidence can be generated by testing the device under evaluation or an equivalent device in the target population for its intended use. The testing methodology should be appropriate to the device characteristics and the intended purpose and may include pre-clinical testing, a clinical investigation, or a clinical performance.

Examples of measures of clinical validation

- Clinical / diagnostic sensitivity
- Clinical / diagnostic specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)
- Number needed to treat (NNT)
- Number needed to harm (NNH)

Figure 7: Clinical Validation

In addition to the three key components described above, clinical/performance evaluation of a device must also consider the benefit-risk ratio in light of the state-of-the-art related to the medical practice for diagnosis, treatment, or patient management.[22]

Independent Review of SaMD/MDSW's Clinical Evaluation

As part of the risk-based approach, and subject to individual jurisdiction's laws, independent clinical evidence review (by a third party) of certain high-risk devices is performed to provide users confidence in the device performance metrics. The significance of an independent review and the level of clinical evaluation should be proportionate to the risk that the device poses.[18,20]

Real-World Device Performance Data

After the initial market release, monitoring the real-world performance data can provide supporting or strengthening evidence for the clinical association of the device output to a clinical condition and may provide evidence that a device's analytical or clinical performance is superior, or inferior compared to the performance metrics initially evaluated by the device manufacturer.[18,20,22]

Such data may include post-market information such as complaints, direct user feedback, Post-Market Clinical Follow-up (PMCF) or Post-Market Performance Follow-up (PMPF) data, new research publications, or guidelines.

5. Challenges of Software Medical Devices

As software is a unique type of medical device, there are unique regulatory, technical, and healthcare challenges associated with it.

Regulatory Challenges:

As software developers are not used to adhering to compliance criteria for medical devices established by the EU, US, and other international regulatory bodies, manufacturers/programmers/developers face various challenges like additional research and development costs.[26] Thus, bringing those software to the market that are supposed to reduce the cost of healthcare becomes a costly affair that slows the time to market and hampers innovation.[27]

Another challenge with software is that they are intended to be updated, changed, and maintained frequently following a product launch. However, no medical device regulation has the provision to accommodate the frequent software upgrades. Hence, a more dynamic regulatory approach that can account for changes during the lifecycle of a device is required. In practice, balancing the need for both business agility and regulatory compliance can be challenging in order to prevent delays in device approvals and recalls.[28]

In addition, fitting certain medical device software within the existing regulatory classification scheme seems challenging.[29]

Technical Challenges:

The sensitive data is made available via the network by software acting as a medical device. The difficulty lies in maintaining the product's functionality and efficiency while protecting the data safety. Cybersecurity flaws may pose risks during medical device use by allowing an attacker to remotely take control of the device, change its functioning and affect the device's safety or performance, or disclose confidential information. Because the internet is dynamic, it is very difficult to eliminate security problems while still making the product responsive to the changing internet. The main challenge is to strike a balance between innovation and adaptation without compromising user data.[25,26,27]

Artificial intelligence is already improving several software medical device applications in the field of image-based healthcare by continuously learning from the data that is sent into the software. Medical device regulations were not meant for these unconventional technologies. Knowledge of and adherence to compliance standards for AI and ML are essential to ensure there are no unexpected consequences.[28]

Healthcare Challenges:

Doctors are typically excluded from the app development process and many app developers have limited or no formal medical training, making it probable that they are unaware of the risks to patient safety that are emphasized by unsuitable app content or functionality.[30]

Due to a lack of software knowledge and time to adequately explain the device's usage, healthcare practitioners also found it difficult to prescribe software medical devices to the patients.[26]

Software applications for accessing information are very helpful. However, access to the correct and/or accurate information through proper data validation, integrity, and quality is often a challenge for various diagnosis and treatment options.[26] In addition, identifying, understanding, and developing the correction and prevention approaches for software errors is often a challenging part.[31]

The post-Corona Virus Infectious Disease (COVID) era, new commercial models, and the ongoing demand for novel patient solutions are some of the additional challenges.[32]

Solutions to Overcome Challenges:

- Regulatory challenges can be overcome by planning development and understanding thoroughly the requirements of each region the SaMD/MDSW is to be marketed in.
- Technical challenges can be overcome by having robust risk management for a SaMD/MDSW to cover and anticipate various risks.
- Healthcare challenges can be overcome by coordinating and working with medical professionals.

6. Conclusion

As software has immensely influenced the healthcare sector, it has provided a vast opportunity for manufacturers to develop innovative products and bring them to the market. The regulations for software medical devices are complex and ambiguous and thus require a team with expertise in applying and deconstructing regulations to ensure compliance and thus assure patient safety. The tech companies (manufacturers) may not have the in-house expertise to keep up with the dynamic regulatory environment as it shifts the focus from their core competency. However, to save time and cost, they can work with consultants to comply with quality management, risk categorization, and clinical evaluation requirements of different geographies.

To strike a balance between innovation and adaptation without compromising the user's data, the risk management for software medical devices must consider risks related to patient safety as well as the data privacy. An effective cybersecurity strategy can mitigate all the possible cybersecurity risks during device development and throughout its lifetime.

The innovations have also created a demand for qualified and trained healthcare professionals for optimal utilization of software medical devices. The benefits of software medical devices in the healthcare sector are enormous provided the manufacturers can navigate the complex and dynamic regulatory requirements to ensure compliance throughout the product lifecycle. Overcoming the current technical and regulatory challenges may take time. However, the future of healthcare looks bright with the simultaneous evolution of software technologies and the regulatory landscape.

Contact Us

We, at ClinChoice, have extensive experience in preparing regulatory (both pre-market and post-market) documents complying with the requirements of different regulatory jurisdictions. If the documents require additional expertise, we collaborate with our in-house clinicians and statisticians. If you would like to discuss any of the points raised in this paper or would need any support in the preparation of regulatory documents for your software or any other medical device at any stage of the device life cycle, please Contact Us.

About ClinChoice

ClinChoice is a leading full-service clinical CRO offering high-quality solutions to pharmaceutical, biotechnology, medical device and consumer products clients. We contribute to a safer and better world by helping our sponsor clients accelerate drug and device approvals to market. We do this by combining our 28 years of proven quality and results with expertise in 30+ therapeutic areas, a flexible approach, and dedicated teams who enable rapid startups and fast timelines.

Our commitment to the highest quality standards, flexibility, and timeline fulfillment has earned us and our clients consistent results. We provide services for the full development lifecycle to a wide range of clients, large and small, including six of the top 10 pharmaceutical companies, as well as small to midsize biotechnology companies. For us, our record of quality means consistency, accuracy and reliability. For you, it means a reliable partner and quality results.

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ClinChoice Inc.
1300 Virginia Drive, Suite 408
Fort Washington, PA 19034 USA
Phone: +1 215 283 6035
Fax: +1 215 283 6382
Email: info@clinchoice.com

ClinChoice
No. 420 Fenglin Road
Floor 11
Xuhui District
Shanghai 430000, China
Email: bd@clinchoice.com

ClinChoice Limited
Suite G48
268 Bath Road, Slough, SL1 4DX
Berkshire, United Kingdom
Phone: +44 1628 566121
Email: europe@clinchoice.com

ClinChoice LLC
3 Barbusse, 0028
Yerevan, Armenia
Phone: +374 60 541515
Email: europe@clinchoice.com

ClinChoice Private Ltd.
#729 8th Main
11th Cross, J.P. Towers
JP Nagar 3rd Phase
Bangalore - 560 076
Karnataka, India
Phone: +91 80 2658 5551
Email: info@clinchoice.com

ClinChoice Inc.
17th Floor
Wynsum Corporate Plaza
22 F. Ortigas Jr. Road, Ortigas Center
Pasig City, - 1605
The Philippines
Phone: +632 8633 5176
Email: info@clinchoice.com

ClinChoice K.K
THE GATE NIHONBASHI Bld.
3FHigashi Nihonbashi 3-4-1,
Chuo-ku
Tokyo 104-0031 Japan
Phone: +81 3 6228 7360
Email: japan@clinchoice.com

ClinChoice Canada Inc.
2 Robert Speck Pkwy
Mississauga, ON L4Z 1H8, Canada
Phone: +1 215 283 6035
Email: info@clinchoice.com

CROMSOURCE
A ClinChoice Company
Via Giorgio De Sandre, 3
37135 Verona - Italy
Phone: +39 045 8222811
Email: cromsource@cromsource.com