

Provisional Translation (as of May 2026)*

Administrative Notice
June 5, 2024

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Medical Device Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Publication of Guidance for Appropriate and Prompt Approval and Development Based on
the Characteristics of Software as a Medical Device (Second Version)

From the viewpoint of more efficient development and regulatory approval of software as a medical device, the ideal regulatory approval system suited to the characteristics of software as a medical device was organized in the "Project to Investigate Improvement on Operation of Regulatory Approval System Based on the Characteristics of Software as a Medical Device" (representative of the project: Shohei Nakano, Executive Director, Japan Association for the Advancement of Medical Equipment) and indicated as "Guidance for Appropriate and Prompt Approval and Development Based on the Characteristics of Software as a Medical Device" on May 29, 2023.

Recently, we have compiled "Guidance for Appropriate and Prompt Approval and Development Based on the Characteristics of Software as a Medical Device" (second version), taking into account matters such as the requirements for the reliability of real-world data, the utilization of clinical evaluation reports for a two-stage approval, and the issues related to the use of data obtained from specified clinical trials for regulatory approval applications in the "Project to Review the Data Reliability, etc. in Regulatory Approval of Software as a Medical Device" (representative of the project: Shohei Nakano, Executive Director, Japan Association for the Advancement of Medical Equipment).

Therefore, please make arrangements so that the guidance will be used as a reference when developing software as a medical device and will be disseminated to marketing authorization holders under your jurisdiction.

We also add that the same administrative notice has been sent to the Japan Federation of Medical Devices Associations, the American Medical Devices and Diagnostics Manufacturers' Association, the EBC Medical Equipment/IVD Committee, the Japan Pharmaceutical Manufacturers Association, the Japan Digital Health Alliance, the Japan Medical Venture Association, the Council for AI Medical Devices, and the Pharmaceuticals and Medical Devices Agency.

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail

Guidance for Appropriate and Prompt Approval and Development Based on the Characteristics of Software as a Medical Device

[Second Version]

March 2024

Preface

Medical devices are modified and improved frequently and in various aspects. When developing a medical device, it is required to consider the necessity of clinical trials and their design including sample size based on the characteristics of each device.

To develop such medical devices more efficiently, we developed guidance for clinical trials in "A Study of Ideal Clinical Trial Guidance Necessary for Prompt and Appropriate Approval and Development of Medical Devices" (representative of the project: Shohei Nakano, Executive Director, Japan Association for the Advancement of Medical Equipment) and in FY 2016 Japan Agency for Medical Research and Development expenditures for sponsored research (Research on Regulatory Science of Pharmaceuticals and Medical Devices). Also, "Release of Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017, hereinafter referred to as the "Clinical Trial Guidance") was published. At the same time, handling of cases in which it is considered possible to file an application for approval of a medical device with or without conducting new clinical trials before marketing was published with "Handling on the Scope of Situations Where "Documents Related to Clinical Study Results" Is Necessary on Medical Devices (Operations Based on Measures Through Pre-and Post-Marketing Phases)" (PSEHB/MDED Notification No. 1117-1 and PSEHB/PSD Notification No. 1117-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017, hereinafter referred to as the "Rebalance Notification").

For software as a medical device, the framework of medical device regulations was newly established in which standalone software could be subject to distribution regulations in accordance with the revised Pharmaceutical Affairs Law promulgated on November 27, 2013 (enforced on November 25, 2014) (renamed to "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices," hereinafter referred to as the "Pharmaceuticals and Medical Devices Act"). Since then, a certain period of time has passed in Japan, and research and development have been actively conducted not only in companies but also in academia. In particular, in the past few years, we have witnessed prominent innovations from Japan, which was not seen in the past, such as the world's first software as a medical device launched by a Japanese company, and it is more necessary to provide such software to the clinical practice in Japan more rapidly.

Software as a medical device is characterized by frequent and diverse methods for its modification and improvement. From the viewpoint of more efficient development and regulatory approval, we have recently decided to organize issues for prompt and appropriate regulatory approval of software as a medical device with assured efficacy and safety.

Given the fact that software as a medical device is less likely to cause significant problems in safety than conventional medical devices, this report was prepared by investigating and considering the ideal regulatory approval system suited to the characteristics of software as a medical device and compiled in consultation with industry-academia-government personnel as practical guidance, including the summary of the progress of discussion and concept, in order to clarify the handling of cases where an approval application can be made early even in a development stage different from conventional medical devices by implementing consistent measures to ensure safety and efficacy from pre- to post-marketing phases with reference to the concept of the Rebalance Notification.

Principal researcher
Shohei Nakano, Japan Association for the Advancement of Medical Equipment

Issuance of the second version

The first version of the guidance was compiled by the Study Group for Improvement of Approval Review Operations for SaMD by the "FY 2022 Project to Investigate Improvement on Operation of Regulatory Approval System Based on the Characteristics of Software as a Medical Device" by the Ministry of Health, Labour and Welfare, and issued as the administrative notice "Publication of Guidance for Appropriate and Prompt Approval and Development Based on the Characteristics of Software as a Medical Device" on May 29, 2023 by the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare.

Then, in September 2023, the "Digital Transformation Action Strategies in Healthcare for Software as a Medical Device 2" was published. In addition, the handling and operation of this guidance were clarified in the "Handling of Two-Step Approval Based on the Characteristics of Software as a Medical Device" (PSB/MDED Notification No. 1116-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated November 16, 2023). Because of further social expectations for software as a medical device, although it was less than one year from the issuance of the first version of the guidance, the second version, which added necessary revisions to the first version, was completed after the investigation by the Study Group on Data Reliability, Etc. in Regulatory Approval of SaMD in "FY 2023 Project to Review the Data Reliability, etc. in Regulatory Approval of Software as a Medical Device" by the Ministry of Health, Labour and Welfare.

The main points of revision in the second version are the following three items.

- Handling of the following unsolved issues in the first version was clarified and described: [1] Requirements for the reliability of real-world data, [2] Forms and manuals for clinical evaluation reports for two-step approval, and [3] Use of data obtained in specified clinical trials for application for regulatory approval.
- The following revisions were made to promote the understanding of developers mainly in "2.2. General Principles for Considering Development Strategy Taking Into Account the Viewpoint of Approval Review": addition of documents, figures, and tables; addition of sections not included in the first version, such as "Handling of Clinical Evaluation for Off-label Use," "Preparation of Submission Data in Accordance With Integrity Standards," and "Use of PMDA Consultations"; and addition of the latest administrative measures, etc.
- An outline of the existing process for development and approval of software as a medical device was newly described in the Appendix, and this revision is intended to supplement the concept shown in this guideline with case examples.

The second version summarizes the results of an industry-academia-government study of the front line of development and approval based on the characteristics of fast-evolving software as a medical device. We expect that the second version of this guidance will lead to the social implementation of software as a medical device beneficial to patients.

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1. Introduction

1.1. Background and Objectives

The revised Pharmaceutical Affairs Law, promulgated on November 27, 2013 (enforced on November 25, 2014) (renamed to "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices," hereinafter referred to as the "Pharmaceuticals and Medical Devices Act") newly established the framework of medical device regulations in which standalone software could be subject to distribution regulations. Since then, the amount of software as a medical device has been increasing every year.

Under this circumstance, in November 2020, the "Digital Transformation Action Strategies in Healthcare for Software as a Medical Device," or DASH for SaMD, was established as a drastic reform for reviews of state-of-the-art software as a medical device. DASH for SaMD promotes early practical use of software as a medical device by recognizing the seeds early, showing the principles in reviews, unifying the consultation service covering from development to reimbursement price, and establishing a review system/structure based on the characteristics of software as a medical device.

Specifically, in April 2021, the "Office of Software as a Medical Device Evaluation" was established in the Medical Device Evaluation Division, Ministry of Health, Labour and Welfare, the Office of Software as a Medical Device (SaMD Office) was established in the Pharmaceuticals and Medical Devices Agency (PMDA), the "Software as a Medical Device Subcommittee" was established under the Medical Devices and In Vitro Diagnostics Committee of the Pharmaceutical Affairs and Food Sanitation Council, and the "Subcommittee on Software as a Medical Device Utilizing AI and Machine Learning" was established in the PMDA Science Board in July 2022. These committees are intended to reinforce the system by newly establishing a specialized division for software as a medical device. At the same time, the development of software as a medical device is characterized by a partial difference in stakeholders from conventional medical devices. Therefore we have recognized that it is necessary to have a place to share information and exchange opinions honestly between the industry and academia developers and personnel of the regulatory authorities for solving the issue and have made efforts for mutual understanding between these parties by holding a forum for the industry, academia, and government collaboration for SaMD (hosted by the Ministry of Health, Labour and Welfare and the Ministry of Economy, Trade and Industry). Furthermore, in September 2023, a new strategy "Digital Transformation Action Strategies in Healthcare for Software as a Medical Device 2" was established based on the "Follow-up of Growth Strategies, Etc." (cabinet decision in June 2023).

In this way, there have been active efforts to promote the practical use of software as a medical device and to establish the development environment. In this situation, we compiled the guidance in the "FY 2022 Project to Investigate Improvement on Operation of Regulatory Approval System Based on the Characteristics of Software as a Medical Device" by the Ministry of Health, Labour and Welfare, and also revised the guidance in the "FY 2023 Project to Review the Data Reliability, etc. in Regulatory Approval of Software as a Medical Device" to further support appropriate and prompt approval and development based on the characteristics of software as a medical device.

The objective of this guidance is to promote the development of software as a medical device in Japan by sharing currently considered common issues in approval reviews of such products among the industry, government, and academia in order for the industry and academia to achieve more efficient commercialization of software as a medical device.

It is hoped that this guidance will serve to optimize the time and resources to be spent in the development and review of software as a medical device by having a common understanding among the government, academia, and industry, and that better products of software as a

medical device will be launched earlier.

1.2. Positioning of Guidance

This guidance supports the principles provided in the "Notice Concerning the Publication of Guidance Materials Concerning Application for Marketing Approval of Medical Device Software" (Administrative Notice of the Office of the Director, Medical Device and Regenerative Medicine Products, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2016, hereinafter referred to as the "Approval Application Guidance") and the Clinical Trial Guidance. In addition, given the fact that software as a medical device is less likely to cause significant problems in safety than conventional medical devices, this guidance is intended to clarify the handling of cases where an approval application can be made early even in a development stage different from conventional medical devices by implementing consistent measures to ensure safety and efficacy from pre- to post-marketing phases with reference to the concept of the Rebalance Notification.

We have investigated and examined the ideal regulatory approval system based on the currently considered characteristics of software as a medical device. As a result, we aim to establish practical guidance for the following development strategy (hereinafter referred to as the "Concept of Two-Step Approval") for software as a medical device: even when the use of the finally targeted product in clinical practice has not established the benefits or values of patients obtained from the treatment, diagnosis, etc. (hereinafter referred to as the "clinical significance"), an approval limited to the intended use or indications that can be shown by the past clinical results or study results for functions or performance is granted and then an application for approval of partial changes is made as needed after the clinical evidence is established based on the experiences of use in clinical practice. Then, based on the results of examination by this guidance, the handling and operation have been clarified in "Handling of Two-Step Approval Based on the Characteristics of Software as a Medical Device" (PSB/MDED Notification No. 1116-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated November 16, 2023).

In light of the characteristics of software as a medical device, this guidance may be revised for some reasons including future technological innovations and accumulation of knowledge. Therefore, it is necessary to take flexible actions with scientific rationality in the development and approval of software as a medical device while understanding the characteristics of individual products.

It is also recommended that from the early stage, the applicant should advance the development of software as a medical device while solving the problems related to development and approval application by utilizing various PMDA consultation systems where necessary.

It is not necessary for all software as a medical device product to be launched through the Concept of Two-Step Approval, and this concept is one of the choices, and the applicant can obtain pharmaceutical approval without employing this approach.

Therefore, as the basic principle for approval and development of software as a medical device in general, "Integrated Principles on Appropriate and Prompt Approval and Development of Software as a Medical Device" is summarized in the next chapter.

1.3. Definition of Terms

The terms used in this guidance are defined as follows.

- **Software as a medical device**
The term refers to software as a medical device based on the Pharmaceuticals and Medical Devices Act used for disease diagnosis, disease treatment, or disease prevention (including media recording the software) stipulated in Attached Table 1 of the Order for Enforcement of the Pharmaceuticals and Medical Devices Act (Government Ordinance No. 11, 1961), excluding those that are unlikely to affect human life or health even if an adverse reaction or malfunction occurs. In Japan, a product marketed as standalone software (falling under the category of a medical device) is called "medical device software" and a product including media recording the software is called "software as a medical device."

- **SaMD**
It is the abbreviation of software as a medical device. "Software as a Medical Device (SaMD): Key Definitions (December 2013)" of International Medical Device Regulators Forum (IMDRF) defines it as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device." That is, it means the "medical device software" in Japan.

- **Rebalance Notification**
"Handling on the Scope of Situations Where "Documents Related to Clinical Study Results" Is Necessary on Medical Devices (Operations Based on Measures Through Pre-and Post-Marketing Phases)" (PSEHB/MDED Notification No. 1117-1 and PSEHB/PSD Notification No. 1117-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017)

- **Clinical Trial Guidance**
"Release of Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017)

- **Software Fundamental Notification**
"Handling of Medical Device Software" (PFSB/MDRMPE Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29 by the Counsellor of Minister's Secretariat (for Medical Device and Regenerative Medicine Product Evaluation), Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, and the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014)

- **Approval Review Guidance**
"Notice Concerning the Publication of Guidance Materials Concerning Application for Marketing Approval of Medical Device Software" (Administrative Notice of the Office of the Director, Medical Device and Regenerative Medicine Products, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2016)

- Administrative Notice for Description Examples (Approval/Certification Application Edition)

"Description Examples of Application Forms and Submission Data for Marketing Approval (Certification) of Medical Device Software" (Administrative Notice of the Office of the Director, Medical Device and Regenerative Medicine Products, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2015)
- IDATEN Fundamental Notification

"Description Examples of Application Forms and Submission Data for Application for Change Plan Confirmation for Software as a Medical Device" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated December 22, 2023)
- Administrative Notice for Description Examples (IDATEN Edition)

"Description Examples of Application Forms and Submission Data for Application for Change Plan Confirmation for Software as a Medical Device" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated December 22, 2023)
- Applicability Guideline

"Partial Revision of Guideline for Medical Device Applicability of Software" (PSEHB/MDED Notification No. 0331-1 and PSEHB/CND Notification No. 0331-4 by the Director of Medical Device Evaluation Division and the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2023)
- Notification 0929

"Handling of Performance Evaluation Tests of Diagnostic Medical Devices Using Existing Medical Imaging Data Without Additional Invasiveness/Intervention" (PSEHB/MDED Notification No. 0929-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated September 29, 2021)
- Registry Fundamental Notification

"Basic principles on Utilization of Registry for Applications" (PSEHB/PED Notification No. 0323-1 and PSEHB/MDED Notification No. 0323-1, by the Director of Pharmaceutical Evaluation Division and the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2021)
- Registry Reliability Notification

"Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications" (PSEHB/PED Notification No. 0323-2 and PSEHB/MDED Notification No. 0323-2, by the Director of Pharmaceutical Evaluation Division and the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2021)

2. Integrated Principles on Appropriate and Prompt Approval and Development of Software as a Medical Device

2.1. Necessity of Considering Approval and Development Together Based on the Characteristics of Software as a Medical Device

In order to continuously create software as a medical device, it is important for the applicant, marketing authorization holder, to take the initiative to provide software as a medical device that can be used in clinical practice, to formulate development strategies in anticipation of post-approval sales strategies and insurance reimbursement, and to implement efficient development¹ assuming the total life cycle of software as a medical device including the post-marketing phase.

Consequently, the applicant should appropriately evaluate the characteristics of the software as a medical device to be developed and to examine the use cases in consideration of the actual status of clinical practice. In doing so, it is necessary to understand the following two axes for responding to medical device regulations: "2.2 Perspective of Considering a Development Strategy Taking Into Account the Viewpoint of Approval Review" and "2.3 Perspective of Available Regulatory Approval System and Further Acceleration." They are outlined in this chapter.

2.2. General Principles for Considering a Development Strategy Taking Into Account the Viewpoint of Approval Review

2.2.1. Basic Perspective

In order to consider a development strategy taking into account the viewpoint of approval review for software as a medical device, the applicant needs to understand the organization of "Conceptual Requirements," common issues, and matters to be described in approval application forms and submission data.

a. Organizing the Essential Part of Data Package "Conceptual Requirements"

When developing software as a medical device, it is important to organize the clinical positioning, design concept, and other aspects for the software as a medical device under development and to arrange the "Conceptual Requirements" based on the differences from already-approved medical devices. The "Conceptual Requirements" can be referred to as the essential part of a data package which the PMDA considers necessary for granting marketing approval, such as what studies are necessary for development and whether clinical trials are required. That is, if the "Conceptual Requirements" are organized, the applicant can clarify endpoints when evaluating the efficacy/safety necessary for approval application.

Therefore, organizing "Conceptual Requirements" before or at the early stage of development of software as a medical device prevents the return of the development stage and thereby enables prompt and efficient approval and development. In particular, this is the most important point when considering a development strategy based on the viewpoint of approval review of software as a medical device, such as whether to select the regulatory approval application in accordance with the Concept of Two-Step Approval or to make a

¹ In viewing the total life cycle of software as a medical device, the "Success Sugoroku Research and Development Steps (in Japanese)" by the Japan Agency for Medical Research and Development can be used as reference.
https://www.amed.go.jp/program/list/02/sangaku_pamphlet.html#success

regulatory approval application without using this approach.

The principle of organizing "Conceptual Requirements," which is necessary to proceed with approval reviews, is outlined below.

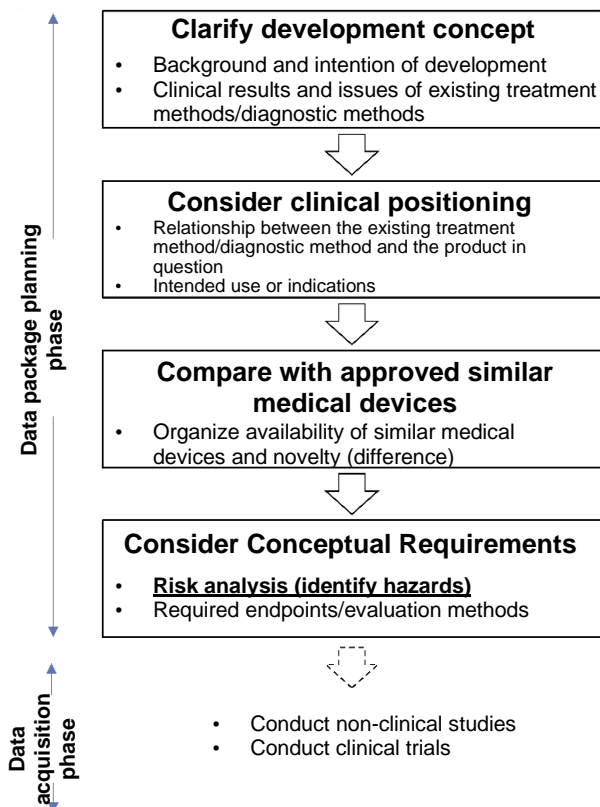


Figure 1. Procedure for Organizing "Conceptual Requirements," Which Serves as the Essential Part of Data Package

[1] Clarify Development Concept

Clarify the intent of the product to be developed or under development based on the background and history leading to the development, natural history of the target disease (availability of existing therapy and course of treatment with existing therapy), actual medical practice (clinical results), severity of the disease, and the latest development status in Japan and overseas.

[2] Consider Clinical Positioning

Clinical positioning of software as a medical device is an important factor in determining the necessity of clinical trials and the study design and the primary endpoint in planning the clinical trials. In addition, the clinical positioning is related to the background of development in the data attached to the marketing approval application form, materials for face-to-face consultation, and "intended use or indications," which particularly shows the characteristics of the approved medical device, and thereby has a major impact on the post-marketing sales strategy. "Clinical positioning" means differences in performance or priority in treatment for the developed software as a medical device regarding why the software is used and what effects it has for the condition of the disease or the patient when compared with other treatment/diagnostic method, and also determines the characteristics of the medical device.

Table 1. Items and Points for Organizing the Clinical Positioning

	Disease diagnostic software	Disease treatment software
What is the target disease or who are the target patients?	Confirmation of the severity of the disease, time of onset of the disease (e.g., acute phase, chronic phase), time of intervention by the product, availability of other treatment/diagnostic options, etc.	
What is the current status of medical care for the target disease/target patients and what are the issues?	Organization of information that quantitatively explains issues from sources such as guidelines and literature.	
Who will use the product for whom?	Clarification of specialist physicians, non-specialist physicians, co-medical, patients, etc.	
How will the software under development resolve the issue? *Does the software apply to any in the right column?	<ol style="list-style-type: none"> [1] Does the software replace existing methods? [2] Does the software enhance efficacy by concomitant use? [3] Can the software help to make a (early) diagnosis noninvasively or minimally invasively compared to existing diagnostic methods? [4] Does the software support existing methods? [5] Does the software provide a new diagnostic method for a disease with no available diagnostic methods? [6] Does the software reduce the burden on healthcare professionals? etc. 	
What and how will the software under development change by being introduced in clinical practice? *Organize the points in the right columns.	<ul style="list-style-type: none"> • How is the current treatment flow being implemented? How will the treatment flow change by introducing the product and where will it be positioned in the treatment flow? • What are the medical benefits for patients? 	<ul style="list-style-type: none"> • What are the medical benefits for patients, such as reducing mortality, improving function, relieving symptoms, improving quality of life, and reducing the probability of loss of function? • Does the effect correspond to either symptomatic therapy or radical treatment? • What is the intended change regarding the probability of obtaining effects and safety compared with existing treatments? • What is the intended change regarding the persistence of efficacy compared with existing treatments?

In order to organize the "clinical positioning," it is important that the product is checkable and easily understandable for a third party² as much as possible based on the relationship between the existing therapies/diagnostic methods and the product (e.g., the novelty and the improved point of the product, whether the product is used as an alternative to, in combination with, or as a supplement to the existing therapies/diagnostic methods) and what clinical outcomes will improve. For example, in the case of software as a medical device intended to support or aid the treatment of a disease, it is important to clarify, e.g., whether the software is aimed to reduce mortality, improve function, ameliorate or alleviate symptoms, improve quality of life, or decrease the probability of functional loss. In addition, in the case of software as a medical device intended to support the diagnosis of a disease, it is important to clarify, e.g.,

²The term "third party" here refers to PMDA in a narrow sense, but in a broad sense it includes a wide-ranging concept including related companies other than the marketing authorization holder, researchers, and supporters of public funds.

whether the software is aimed to detect and confirm a disease, predict its onset, diagnose a disease, or identify patients who are likely to respond to a certain treatment method.

The key factor to ensure that the product is checkable and easily understandable for a third party is to organize the "clinical positioning" based on the "development concept" referring to Table 1 "Items and Points for Organizing the Clinical Positioning."

As described in Section 2.4.3, there has been no approval granted for disease prevention software. However, it is also possible to organize the clinical positioning using the concept for disease diagnosis software or disease treatment software.

[3] Compare With Approved Medical Devices

If the product under development has a similar medical device, not limited to software as a medical device, the applicant needs to organize the information on the product under development by comparing it with the similar medical device. For how to compare similar medical devices, refer to "Points to Consider in Preparing Data Attached to Application Form for Marketing Approval of Medical Devices" (PFSB/MDRMPED Notification No. 0120-9 dated January 20, 2015).

[4] Consider Conceptual Requirements

The "Conceptual Requirements" refers to evaluation items necessary for assessing the clinical efficacy/safety of software as a medical device under development. Based on the above [1] to [3], the Conceptual Requirements for the product under development should be organized to consider appropriate evaluation methods based on the development concept and characteristics of software as a medical device. In addition, for the difference from approved medical devices (including software as a medical device), the applicant needs to perform risk analysis considering the items of difference and the characteristics of the product under development and to perform necessary evaluation.

Table 2 shows rough examples of "Conceptual Requirements" to be shared for software as a medical device. They can be used as a reference because individual cases are also introduced in the later-described "Points of Review of Medical Device Software." However, the applicant needs to note that individualization is always required based on the characteristics of the software as a medical device under development.

Software as a medical device with high novelty should be discussed and evaluated from various perspectives to ensure clinical efficacy and safety while employing existing evaluation methods.

Table 2. Examples of Conceptual Requirements for Software as a Medical Device

Type of software as a medical device	Conceptual Requirements
Disease diagnostic software	<ul style="list-style-type: none"> • The product uses the results of analysis on the intended input data to improve diagnostic performances of target users. • The product is able to have a clinically significant detection and differentiation performance for the intended input data. • The product is able to complete processing within a clinically acceptable time frame.
Disease treatment software	<ul style="list-style-type: none"> • The product can improve symptoms in intended users at a level showing clinical significance.
Common to disease diagnostic software and disease treatment software	<ul style="list-style-type: none"> • Other functions (e.g., input, output, screen display) operate as intended. • The usability engineering process is properly controlled. • The software development life cycle process is appropriately controlled. • Actions for cybersecurity are appropriately taken.

b. Issues in Approval Review

[1] Function and Performance of the Proposed Product

In approval reviews, the applicant needs to organize and explain in detail what function and how much performance the developed product has (design concept) based on the development concept. Since the clinical positioning for which the applicant would like to obtain approval determines the functions and performance necessary or required for the product under development, the concept of the developer should be clarified taking into account the actual medical practice and clinical positioning. The functionalities to be checked in approval reviews are not intended only for the functions necessary to demonstrate clinical efficacy, but are aimed for all functions that the proposed product has.

The applicant should also explain the requirements for input information, platform requirements, and use environment requirements necessary for processing input data with appropriate precision based on the user, usage method, and other conditions. For example, when a wearable device with a sensor (including a non-medical device) is used as a platform, the precision control of the sensor is important for obtaining appropriate data such as the number of steps, walking distance, amount of exercise, camera image information, and voice information. Therefore, even in the development of software as a medical device, it is necessary to consider the requirements for the device to be used together. In addition, as a developer of software as a medical device, the applicant needs to explain that the safety for patients and users (e.g., electrical safety, electromagnetic compatibility) is ensured when the platform on which the software as a medical device is installed is used in the environment of clinical practice.

If software as a medical device processes information input from other medical devices or outputs data to other medical devices, or if the software is expected to be used in combination with drugs, conditions for the medical device expected to be used together should be identified, and the necessity of joint development of such a medical device and regulatory procedures should be discussed with the marketing authorization holder of the medical device in question to take actions.

If the applicant develops software as a medical device using various data provided by public organizations, such as weather observation data provided by the Japan Meteorological Agency, the assurance of the reliability of such data will be an issue. Therefore, it is desirable to consult the PMDA in advance at the early stage of development regarding the validity of

methods³ related to information collection by public organizations and the management system for such information.

[2] Function, Principle and Algorithm as a Product

The applicant needs to explain the software as a medical device regarding what principles and algorithms are used for the processing of input information (including the details of processing, assessment criteria, and cutoff values), input condition for normal processing of input information, and what information is output after algorithm processing. In particular, if machine learning is used, it is important to clarify what kind of learning algorithm and what kind of development data are used (data collection facilities, how to set the correct label, how much the learning data is) (Figure 2).

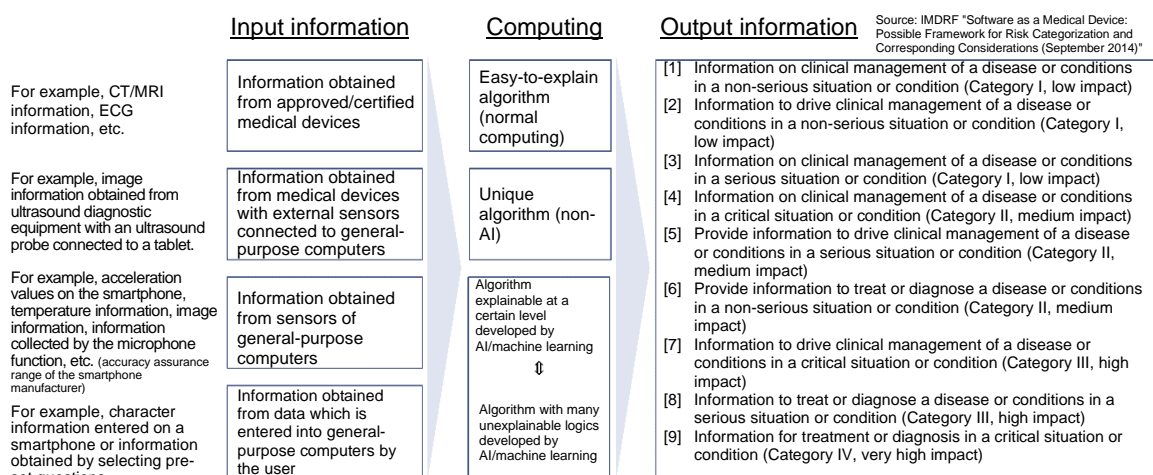


Figure 2. Concept of Input Information, Computing, and Output Information of Software as a Medical Device

[3] Evaluation of Each Function of the Product

For the functions clarified in [1] above, the applicant needs to evaluate the software's operation as intended by the developer.

³ For example, the meteorological observation data provided by the Japan Meteorological Agency are observed/measured in accordance with the Meteorological Observation Statistics Guideline. This guideline is not only the "technical standards for statistics on meteorological observation performed by the Japan Meteorological Agency", but also positioned as a "manual for conducting various statistics using basic weather observation statistics materials provided by the Japan Meteorological Agency", and may serve as a rationale for the reliability of data.

On the other hand, school health checkups based on the School Health and Safety Act are conducted in accordance with the manual for medical checkups for school children (supervised by School Health Education Division, Sports and Youth Bureau, Ministry of Education, Culture, Sports, Science and Technology, issued by the Japan Society of School Health, revised in 2015). However, it is unknown whether there are clear rules about how to manage the acquired data. At present, some organizations have databases of anonymized personal information derived from school health checkups conducted based on the School Health and Safety Act under a contract with local governments nationwide, but direct provision from public institutions cannot be confirmed.

[4] Examination of the Necessity of Clinical Trials

(1) Evaluation of Data Sufficiency

Whether or not software as a medical device needs to conduct clinical trials is determined based on the degree of novelty as software as a medical device and the details of evaluation necessary for evaluating the efficacy and safety. Taking into account the development concept, clinical positioning, differences from already-approved similar software as a medical device, and Conceptual Requirements, clinical evaluation will be conducted comprehensively based on the results of non-clinical studies such as performance tests and animal studies, existing clinical data, and literature. If something that can only be evaluated in a clinical trial remains unevaluated, conducting a new clinical trial is required (Table 3).

On one hand, for software as a medical device for disease diagnosis for which the clinical significance has already been established or the clinical efficacy and safety have been verified with respect to the software and its output information, it may be possible to evaluate the efficacy and safety by performance tests using existing medical image data without additional invasiveness or intervention even if a clinical trial is not conducted as described below.

On the other hand, even for software as a medical device for which submission of clinical study data is required, clinical evaluation may be possible without conducting a new clinical study if a clinical evaluation report that explains a certain level of public knowledge enough to substitute for clinical studies can be prepared.⁴ by comprehensively collecting and evaluating literature, etc. in order to evaluate the efficacy and safety of the product in question.

Table 3. Rough Guide for Evaluation Policy According to Clinical Positioning

Development concept	Clinical positioning	Matters that need to be shown in non-clinical studies	Necessity of a clinical trial	Matters that need to be shown in clinical studies
New therapy	Provide a new treatment method for a disease without available effective treatment	Study setting and verification according to the development concept	Necessary in principle	Superiority to existing treatments
Improvement of existing products	Improve efficacy, reduce risk, or improve usability	Superiority to approved products	Necessary if evaluation is not possible by non-clinical studies	Superiority or non-inferiority to approved products
Equivalent to existing products	Provide device options	Equivalence to approved products	Necessary if evaluation is not possible by non-clinical studies	Non-inferiority to approved products

(2) Evaluation by Performance Tests Using Existing Medical Image Data Without Additional

⁴ When preparing a clinical evaluation report, refer to "Guidance for Preparation of Clinical Evaluation Reports and Materials for Clinical Evaluation Consultation Part 1 (November 2020)" and its "Part 2 (May 2023)" published by the Japan Federation of Medical Devices Associations. In general, clinical evaluation based on a clinical evaluation report applies to cases in which the product has been used to a certain extent because it has been approved overseas (especially in the United States) or in which the product is publicly known at a certain level, such as listed in clinical practice guidelines or guidelines of academic societies. In the development based on a new concept, the product and its concept are not publicly well known medically and pharmaceutically. Therefore, the applicant should note in advance that it is very unlikely to be able to collect clinical data enough to be used for preparing a clinical evaluation report. For details, see "Decision Categories Emphasized for Acceptance of Clinical Evaluation Reports" in the guidance Part 2.

Invasiveness/Intervention

When considering the evaluation of software as a medical device for disease diagnosis, use of Notification 0929 is assumed if efficacy and safety can be evaluated by performance tests using existing medical image data⁵ without additional invasiveness/intervention.

Faster development is expected when the evaluation data are sufficient in the performance evaluation test which applies to Notification 0929 without newly conducting a clinical trial.

The principle shown in the Notification 0929 may be widely used, and therefore it is recommended for prompt development that the applicant consult the PMDA in advance.

Table 4. Specific Handling of Notification 0929

	(1) Cases where only existing medical image data or biological samples are collected, new information necessary for evaluation is added to them, and the data or samples are used for performance evaluation	(2) Cases where existing medical image data or biological samples and related existing medical information are collected and used for performance evaluation
Application category	Mainly improved medical devices (without clinical data)	Mainly improved medical devices (with clinical data)
Ensuring ethics ⁶	-	○
Ensuring reliability ⁷	○	○ ⁸
Positioning of submission data of approval application	Data on design and development (Article 114-19, Paragraph 1 (i) (b) of the Enforcement Regulation)	Data substituting clinical study results (Article 114-19, Paragraph 1 (i) (f) of the Enforcement Regulation)
Possible cases	Chest CT images are retrospectively collected to evaluate the assessment performance of the diagnostic support image analysis function.	Medical chart information ⁹ with chest CT images and definitive diagnosis results is retrospectively collected to evaluate the assessment performance of the diagnostic support image analysis function

(3) Handling of Results of Clinical Trials Conducted in Foreign Countries

If the efficacy and safety of software as a medical device have been verified in a confirmatory clinical study conducted overseas, the necessity of a Japanese clinical trial to evaluate the efficacy and safety in Japanese subjects will be considered, taking into account ethnic factors (internal and external factors).

For software as a medical device developed overseas with different languages and

⁵ Existing medical image data or biological samples, and related existing medical information (limited to those obtained in regular medical care or shared in biobanks or databases to which such data or samples are provided, excluding data obtained in clinical studies requiring intervention.)

⁶ At the time of approval application, the applicant can explain that patients have appropriately provided consent for provision/disclosure of data used in the study to third parties and commercial use including approval application, based on supporting data, as requested by PMDA. For the appropriateness of consent, refer to the Act on the Protection of Personal Information.

⁷ Appropriate management is implemented to ensure the reliability of data used in the study (e.g., establishing a QC/QA system) and submission data are prepared in accordance with the data integrity standards for product applications specified in Article 114-22 of the Enforcement Regulation.

⁸ The applicant can explain that appropriate management is implemented based on the supporting data at the time of PMDA's GLP/GCP/GPSP Inspections.

⁹ Medical chart information containing the information of definitive diagnosis related to treatment policy after diagnosis, etc.

lifestyles, external factors including the validity of translation, cultural backgrounds, and differences in lifestyle will be the issues. Therefore, the applicant needs to evaluate, before marketing, whether the efficacy and safety equivalent to those in the overseas confirmatory study are shown in the Japanese medical environment and to take more appropriate post-marketing safety measures.

The basic principles for conducting global clinical trials have been shown for drugs and medical devices, and the applicant needs to consider ethnic factors (internal and external factors) for software as a medical device in the same manner. Ethnic factors that should be considered for software as a medical device include the following:

- 1) Internal factors: racial differences (e.g., differences in constitution or thickness of bone, difference in morphology, type of disease, difference in metabolic system for medical devices containing drugs), etc.
- 2) External factors: high novelty of the procedure, differences in concomitant drugs/devices, differences in standard treatment, differences in clinical practice guidelines, differences in medical circumstances (e.g., status of transplantation therapy, degree of spread of similar procedures, differences in qualifications of healthcare professionals, differences in the perspective on therapeutic intervention), differences in social/cultural background, lifestyles, language and literacy rate, IT literacy, health literacy, etc.

On the other hand, given the characteristics of software as a medical device, the applicant should also examine whether factors depending on the information input to and output from the software are taken into account in design as the premise of considering extrapolability of overseas clinical study data.

The examples include how much the variation in input information affects functional and performance differences of software as a medical device between Japan and overseas (e.g., if the input information is skin image information, the color tone adjustment function is considered in design), and if discrepancies in various judgments on the diagnosis of a disease (e.g., discrepancies in the grading of a disease) cause differences in annotation of learning data affecting the output of the software as a medical device (e.g., possible biases in learning data derived from diseases unique to Asians or regionality).

In these cases, the software as a medical device should be carefully used in limited sites and target patients in the post-marketing setting and appropriate data collection and safety measures should be implemented. Through these actions, it is possible that the safe and appropriate use of the software can be ensured without evaluation through pre-marketing clinical trials. These actions may contribute to early introduction of the software as a medical device already approved overseas to Japan. However, if differences in external factors other than language cause a significant concern or uncertainty about safety as well as efficacy, the applicant needs to evaluate risk-benefit balance before marketing and should consider additional Japanese clinical trials.

In addition to the differences between Japan and overseas, it is important that the applicant explains the validity of evaluation with reference to the above 1) and 2) because, in the case of software as a medical device to diagnose a disease by processing speech information from the voice information, dialects may be important as an issue in the evaluation of the software.

A clinical trial is an interventional study in human subjects, which has an investigative aspect and needs assurance of ethics. Also, conducting a clinical trial may require many

hours, costs, and resources. Therefore, in order to efficiently develop software as a medical device, it is important to comprehensively evaluate existing clinical data and literature information, carefully consider what measures can be taken to ensure patient access at an early stage, and identify necessary clinical data. In deciding the necessity of a clinical trial, it is recommended that the applicant use the PMDA pre-development consultation and consultation on necessity of clinical trials based on the discussions in "A Organizing the Conceptual Requirements" and "B Issues in Approval Review." Even if it is considered necessary to conduct a clinical trial for software as a medical device as a result of the consideration of the necessity of the trial, the information referred to in "3. Basic Principles on Clinical Trial Design and Sample Size" and "5. Conduct of Good Clinical Trials and Quality Control of Clinical Trial Data" of the Clinical Trial Guidance may be of benefit to people conducting the clinical trial.

(4) Handling of Clinical Evaluation for Off-label Use

For software as a medical device for physicians that has already obtained marketing approval and used for unapproved intended use or indications or with an unapproved performance, operation method, or use method in a medical setting (so-called off-label use) with sufficient scientific evidence for the off-label use, an application for approval of partial changes or a new approval application (when the term name is different from the approved product) will be required for the intended use or indications related to the off-label use in question in order to enable the proper use in medical practice.

When reviewing data for clinical evaluation required to add a necessary intended use, if the validity of the off-label use is confirmed to be publicly known from the medical and pharmaceutical perspective by any data of the following 1) to 3), a decision on the approval of the intended use in question will be considered based on such data without conducting a new clinical evaluation through a new clinical study. Therefore, the applicant should consult in advance the Office of Software as a Medical Device Evaluation, Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare.

- 1) The product has already been approved for the intended use in question in a foreign country (a country with an approval system that is considered to be at the same level as Japan's or a country with an equivalent system [e.g., the United States]), there is a considerable amount of use results in medical care, and data attached to the approval application submitted to the regulatory authority are available.
- 2) The product has already been approved for the intended use in question in a foreign country, there is a considerable amount of use results in medical care, and there is an article that has been published in an internationally reputable scientific journal and can be a scientific basis or review paper evaluated by an international organization
- 3) There are results of a clinical study whose ethics, scientific nature, and reliability can be confirmed because, e.g., the study is conducted as the contract research of a public research project.

For details, see "Handling of Medical Devices for Physicians Concerning Off-label Use" (HPB/RDD Notification No. 0522001 and PFSB/ELD Notification No. 0522001, by the Director of Research and Development Division, Health Policy Bureau and by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated May 22, 2006).

(5) Handling of Study Results Obtained in Specified Clinical Trials

When an area is in its early days, such as software as a medical device, research and development are often conducted in cooperation with academia. In particular, when the development is based on a new concept, it may be difficult to advance development unless led by academia staff familiar with clinical practice. Among others, exploratory clinical trials are important before conducting a confirmatory clinical trial for stabilizing procedures and therapies, selecting appropriate subjects, and setting appropriate primary endpoints. Under certain conditions, specified clinical trials may be conducted as a substitute for exploratory clinical trials.

In such a case, if prerequisites are established, such as ensuring the reliability at a level comparable to clinical trials, information obtained from specified clinical trials may be used for application for regulatory approval¹⁰. Therefore, if the applicant assumes that a specified clinical trial will be carried out in an exploratory manner before conducting a confirmatory clinical trial in pharmaceutical development, it is desirable to obtain guidance/advice through RS Strategy Consultation by the PMDA¹¹ regarding the overall consistency of the pharmaceutical development strategy under consideration at the time of drawing up the overall study plan.

An increase in the number of specified clinical trials to be conducted in a package that meets the reliability level in advance will contribute to the improvement of the quality of specified clinical trials in the future and also lead to promotion of development of software as a medical device. Therefore, early consultation with PMDA is desirable.

[5] Other Issues Regardless of Individual Products

The basic requirements of medical devices necessitate risk management, ensuring of a development lifecycle process, ensuring of cybersecurity, and ensuring of usability engineering. This section outlines the risk management, software life cycle process, cybersecurity and other issues which are often discussed in particular for software as a medical device.

(1) Risk Management

Based on Article 2 (Risk Management) of the Essential Principles for Medical Devices, risk management is required for all medical devices including software as a medical device, and the corresponding official standard is known as JIS T 14971 (Medical devices-Application of

¹⁰ At present, there is only one case approved based on the study results of Advanced Medical Care B, which correspond to a specified clinical trial (a multicenter study for verification of the efficacy of radiofrequency ablation and its standardization for early breast cancer: RAFAELO study). This case concerns a new medical device (partial change) in which an indication of early breast cancer was added to the approved radiofrequency ablation system (class III) on July 7, 2023. The product was designated as a medical device with high medical needs because there is an expectation for early introduction by academic societies. Taking into consideration the background information such as the status of publication of the obtained study results as a paper and the status of description in related guidelines, this case was comprehensively judged based on the fact that the evaluation was considered to be feasible without conducting a clinical study directly comparing with the standard therapy and the fact that the applicant had built a cooperation structure with the investigator for compliance review in advance and the assurance of reliability equivalent to a clinical trial was confirmed from the compliance document review and on-site inspection.

¹¹ Points to consider when planning clinical studies (clinical trials) of medical devices: if the results of nonclinical studies alone cannot be extrapolated to humans regarding the efficacy and safety of the developed product, these items will be verified by clinical studies (clinical trials). Clinical studies include clinical research or clinical trials conducted in an exploratory manner and confirmatory clinical trials conducted to verify the hypothesis obtained from these clinical trials or research. When clinical study results are attached to a marketing approval application, they must be those obtained from a confirmatory clinical trial, in principle. Excerpted from the guidelines for PMDA Regulatory Science Strategy Consultation and brochures for RS General Consultation/RS Strategy Consultation

risk management to medical devices). Note that this item requires evaluation of not only known hazards but also foreseeable hazards.

When filing an application for approval, the applicant needs to describe the implementation status of risk management and residual risks in submission data.

(2) Software Life Cycle Process

Based on the provisions of Article 12 (Consideration for medical devices using software), Paragraph 2 of the Essential Principles for Medical Devices, it is required to ensure the life cycle process of development for software as a medical device. The applicant needs to explain the compliance with the standards in submission data with reference to JIS T 2304 (Medical device software-Software life cycle processes), etc.

In these standards, the software as a medical device being developed is classified into software safety classes according to the risk of harm that may be caused by the use of the software, and actions according to these classes are required. Since software as a medical device is used in medical practice, it is necessary to classify the product considering that any incorrect output information may cause a hazardous situation.

(3) Cybersecurity

Based on the provisions of Article 12 (Consideration for medical devices using software), Paragraph 3 of the Essential Principles for Medical Devices, it is required to ensure cybersecurity for software as a medical device. The applicant needs to explain the compliance with the standards in submission data with reference to JIS T 81001-5-1 (Health software and health IT systems safety, effectiveness and security-Part 5-1: Security-Activities in the product life cycle), etc.

(4) Principles on Evaluation Samples in Each Study

For both non-clinical and clinical studies, the version of the product used for evaluation should be the one for which the applicant seeks approval in principle. However, for software as a medical device, changes in the external environment, such as an update of OS, may cause frequent modifications and corrections after the product is evaluated. If a study is conducted using a version different from the version for which the applicant seeks approval, the applicant needs to identify the difference and explain the validity of using the version instead of the one for obtaining approval even with that difference.

(5) Issues for Software as a Medical Device Using Machine Learning

In the development of software as a medical device, the applicant needs to eliminate biases of evaluation data to be used in the evaluation study as much as possible and then to examine the variations, taking into account the clinical positioning of the proposed product and the purpose of the study.

On the other hand, supervised machine learning is an AI machine learning method using the characteristic that output changes non-linearly with input information. Thus, unintended results may be output if unknown data not used as learning data during development are computed as input information after launch of the product. In many cases, the principles, algorithm, and design specifications alone, specified in the approval application form, cannot explain that the quality of output information obtained by machine learning is assured. In particular, for products using neural networks by deep learning, even their designers may not be able to fully interpret their behavior.

Therefore, in the evaluation of software as a medical device using machine learning, it is important at present to eliminate bias as much as possible and to confirm that appropriate output information is obtained from evaluation data, which cover the expected range of input, in view of the expected clinical positioning.

The Science Board established in the PMDA prepares policies for handling advanced science/technology-applied products, guidelines, and guidance and makes other proposals for measures to improve scientific aspects of reviews and related services. The discussions at the Subcommittee meetings have been compiled and released as reports. The "Regulatory Science on AI-based Medical Devices and Systems" was released in December 2017. Subsequently, the "Report on AI-based Software as a Medical Device (SaMD)" was released in August 2023. The " Report on AI-based Software as a Medical Device (SaMD) " discusses trends analysis on activities to establish medical device regulations and medical device safety standards in Japan and overseas, various problems of bias in machine learning, issues on reuse of evaluation data in post-marketing learning and current status of research for resolving the issues, current situation and issues of construction of learning data by physical models and simulations, and issues on various clinical information databases as data sources of learning data, verification data, and test data.

(6) Preparation of Submission Data in Accordance with Integrity Standards

Data submitted for marketing approval applications must be collected and prepared in accordance with the standards specified by the MHLW Ministerial Ordinance. The standards specified by the MHLW Ministerial Ordinance include the Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices (GLP for Medical Devices), the Good Clinical Practice for Medical Devices (GCP for Medical Devices), and the data integrity standards for product applications (Integrity Standards). In particular, the Integrity Standards are outlined here.

The Integrity Standards are specified in Article 114-22 of the Enforcement Regulation of the Pharmaceuticals and Medical Devices Act and requires three items: accuracy (the data should be accurately prepared based on study results), completeness and comprehensiveness (if the investigation results suggesting a lack of efficacy or safety are obtained, the results should be examined and described), and preservability (the supporting data should be stored). The submission data should be prepared in accordance with the Integrity Standards and the applicant needs to be able to explain, based on supporting data, that appropriate control is being implemented at the time of PMDA's GLP/GCP/GPSP Inspections (document-based inspections¹² or on-site inspections).

On one hand, in the preparation of data submitted for marketing approval applications, compliance with the Integrity Standards is required as described above. However, compliance with the Integrity Standards is not required in all processes from development to launch of a product. For the algorithm of SaMD, for example, the development process itself does not require compliance with the Integrity Standards. In order to realize efficient development, the applicant needs to make a sharp distinction between the development process and evaluation process (verification for regulatory application) and to understand in advance the scope of compliance with the Integrity Standards.

¹²Points to consider (checklist) for smooth implementation of document-based compliance inspections (non-clinical studies) are introduced by "Points to Consider for Smooth Implementation of Document-Based Compliance Inspection for Medical Devices (Non-clinical Studies)" (Administrative Notice of the Office of Non-clinical and Clinical Compliance, Pharmaceuticals and Medical Devices Agency, dated February 9, 2018).

On the other hand, for the algorithm of SaMD, the development process itself can be divided into the basic research stage before concept decision and the product development stage after concept decision, when considered based on the medical device development management stage gate by the AMED. In the former basic research stage, algorithm development involving trial and error is conducted more freely. In the latter product development stage, it should be noted in advance that the product should be developed with appropriate document control anticipating future regulatory actions, even if compliance with the Integrity Standards is not required.

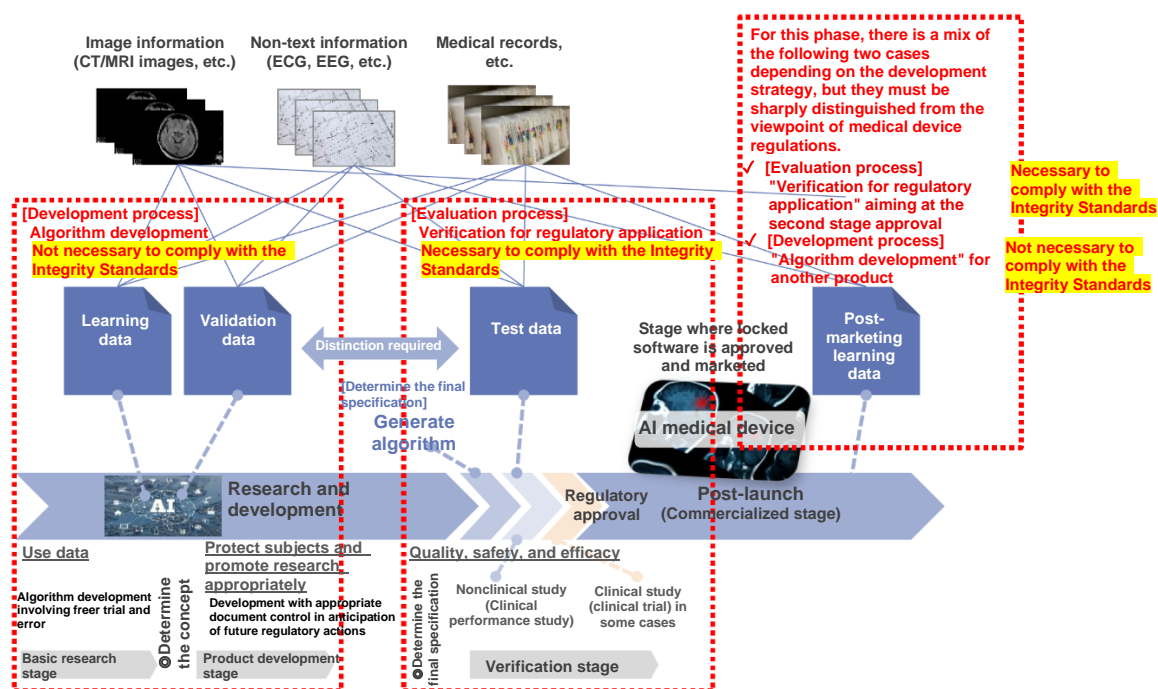


Figure 3. Conceptual Diagram of the Scope Requiring Compliance With the Integrity Standards by the Process of Development and Evaluation

c. Matters to Be Described in the Approval Application Form and Submission Data

In order to ensure the efficacy and safety of the proposed product, the approval application form should include the appropriate descriptions of the intended use or indications, shape, function, structure and principle, and specifications for performance and safety.

Matters to be described in the approval application form for software as a medical device need to be prepared with reference to related notifications such as "8. Handling of Marketing Approval Applications" of the Software Fundamental Notification, Administrative Notice for Description Examples (Approval/Certification Application Edition), and Questions and Answers (Q&A).

In addition to the above notifications, "Medical Device Good Review Practice (GRP)" (June 3, 2016) prepared by PMDA is useful for matters to be described in each column of submission data for software as a medical device.

For software as a medical device approved as a new medical device¹³, information on review reports prepared by the PMDA and data submitted for the application for marketing approval of medical devices are available on the website of the PMDA for reference.

In addition, the general process of development and approval of existing software as a medical device for disease diagnosis or disease treatment is shown in Appendix 1 for reference. The development and approval processes vary greatly depending on the characteristics and novelty of the software as a medical device, development background, non-clinical study results, characteristics of treatment methods, availability of similar products, and availability of data for similar treatment methods. Therefore, it should be noted that these are only specific examples and should be used just as reference data.

2.2.2. Viewpoints by Specific Technology/Product

The Ministry of Health, Labour and Welfare has published technical evaluation indices used for reviews. The ministry has also selected the field of study and released next-generation evaluation indices for the purpose of improving product efficiency and accelerating approval reviews. As evaluation indices for next-generation medical devices related to software as a medical device, the following three guidelines have been published.

- [1] "Publication of Evaluation Indices for Next-Generation Medical Devices: Attachment 3 Software for Blood Flow Simulation" (PSEHB/MDED Notification No. 0523-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated May 23, 2019)
- [2] "Publication of Evaluation Indices for Next-Generation Medical Devices: Attachment 4 Evaluation Indices for Medical Imaging Diagnostic Support Systems Using Artificial Intelligence Technology" (PSEHB/MDED Notification No. 0523-2, by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated May 23, 2019)
- [3] "Publication of Evaluation Indices for Next-Generation Medical Devices: Attachment 2 Evaluation Indices for Medical Device Software That Involves Behavior Change" (PSEHB/MDED Notification No. 0609-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated June 9, 2022)

¹³ At present, review reports and data submitted for the application for marketing approval of medical devices have been published for the following products: sleep disorder software (SUSMED CBT-i App for Insomnia, approved on February 15, 2023), software to control general anesthetic drug administration (Syringe Pump Control Software for Assisting Total Intravenous Anesthesia, approved on September 29, 2022), software to support detection of disease characteristic findings for endoscopy (nodoca, approved on April 26, 2022), hypertension treatment support software (CureApp HT Hypertension Treatment Aid App, approved on April 26, 2022), tumor malignancy assessment support software (Oncotype DX Breast Recurrence Score software, approved on August 6, 2021), gene mutation analysis software (for cancer genomic profiling test)/somatic mutation analysis software (for determining the indication of anticancer drugs) (FoundationOne Liquid CDx Cancer Genome Profile, approved on March 22, 2021), treatment planning software for boron neutron capture therapy (BNCT dose calculation software NeuCure Dose Engine, approved on March 11, 2020), gene mutation analysis software (for cancer genomic profiling test)/somatic mutation analysis software (for determining the indication of anticancer drugs) (FoundationOne CDx Cancer Genome Profile, approved on December 27, 2018), germline mutation analysis software (for determining the indication of anticancer drugs) (BRACAnalysis Diagnostic System, approved on March 29, 2018), and hemodynamic analysis software (HeartFlow FFRCT, approved on November 14, 2016). In addition, DASH for SaMD2 states that review reports on improved medical devices will be prepared and published in the future. Therefore, the development company also needs to always collect reference materials.

None of the evaluation indices is positioned as a legal standard, and the provided evaluation items are for next-generation medical devices with significant technological development. Depending on the characteristics of the product, evaluation may be necessary for items not shown in the evaluation indices or some of the evaluation indices may not be applicable.

The Ministry of Health, Labour and Welfare and the PMDA have been actively involved in the development and revision of certification standards for previously approved software as a medical device, in cooperation with industry. In addition, PMDA presents necessary evaluation items for medical devices included in the predefined category as "review points for medical device software" to contribute to streamline the preparation of documents and accelerate reviews for approval application. As of March 2024, three certification standards and five review points have been developed and published.

Certification standards	Software for radiation planning criteria
	Supporting software for respiratory treatment criteria
	Supporting software for external fixators treatment plan criteria
Review points	Software for Peritoneal Dialysis Treatment
	Supporting Software for Dental Implant Treatment
	Software for Ophthalmic Surgery Treatment Planning
	Supporting Software for Detecting Lesion with Endoscopic Imaging
	Computer-Aided Diagnosis Program to Support Interpretation of Medical Images

The Science Board established in the PMDA prepares policies for handling advanced science/technology-applied products, guidelines, and guidance and makes other proposals for measures to improve scientific aspects of reviews and related services. The discussions at the Subcommittee meetings have been compiled and released as reports. As of March 2024, three certification standards and five review points have been developed and published.

"Regulatory Science on AI-based Medical Devices and Systems" (December 2017)
"Subcommittee Report on Concept of Review of Medical Device Software Using Computer Simulation" (March 2021)
"Report on AI-based Software as a Medical Device (SaMD)" (August 2023)

The scope of published notifications is specified in each document, but the principles for evaluation of software as a medical device may be useful regardless of the software under development. Therefore, it is desirable for the developer and marketing authorization holder to review the contents of such documents for development and approval application.

2.2.3. Changes in Software as a Medical Device

When an approved item (items described in the columns of "Intended Use or Indications," "Shape, Structure, and Principle," or "Specifications for Performance and Safety" of the Approval Document of the medical device) is changed in association with alterations of software as a medical device after approval, an application for approval of partial changes is required if the change affects the efficacy or safety.

On the other hand, examples of cases that require a minor change notification include addition/change/deletion of the type of operating environment OS or a cloud operation, such as change to/addition of a different type of operating environment OS.

Also, examples of cases that do not require any procedures of partial change approval application or minor change notification (no notification required) are shown in the "Handling of Minor Change Procedures in Association With Partial Change of Medical Device Software (PSEHB/MDED Notification No. 1020-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated October 20, 2017)" as follows: Changes, additions, or deletions of OS, which is the operating environment of the medical device software (limited to the cases where the intended use or indications and performance of the medical device are not affected); and additions, changes, or deletions of generic PCs or information terminals recommended as the operating environment. However, when bug fixes or other actions are taken, a recall may be needed depending on their nature, and therefore attention is called by "Questions & Answers About Handling of Medical Device Software (Part 2)" (Office of the Director, Medical Device and Regenerative Medicine Products and Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 30, 2015).

For software as a medical device for which improvement of the performance is expected in the post-marketing setting, such as medical devices using AI, the utilization of the later-mentioned procedure system for change plan confirmation (IDATEN: Improvement Design within Approval for Timely Evaluation Notice) is expected.

As to the procedure for modifying software as a medical device, the applicant can use PMDA simple consultations to determine which of the following the product applies to: partial change approval application, minor change notification, and no notification required.

2.2.4. Use of PMDA Consultations

In order to consider a more appropriate and rapid development strategy based on the viewpoint of approval reviews for software as a medical device, the perspectives described in the previous sections are necessary, and the applicant should preferably use PMDA consultations as soon as possible for unclear points or other issues.

This guidance also describes the current principles and notifications as much as possible. At present, the PMDA website¹⁴ provides common questions in general consultations held by the PMDA (e.g., definitions of software as a medical device, development plan, consultation flow, business license/registration, marketing approval application) as "Frequently Asked Questions About Software as a Medical Device."

¹⁴ The "Frequently Asked Questions About Software as a Medical Device (in Japanese)" is publicly available at <https://www.pmda.go.jp/files/000264780.pdf>. The site is scheduled to be updated as appropriate in response to the issuance of various notifications. Make sure to check the latest version before use.

In order to efficiently and effectively utilize PMDA consultations, it is more important to clarify what the applicant would like to discuss according to individual development products as much as possible than to have a PMDA consultation with the consultation items that contain many general questions. Therefore, it is useful to collect a wide range of information including publicly available information and address it in advance, from the viewpoint of streamlining development.

2.3. Currently Available Regulatory Approval System

The regulatory approval system related to software as a medical device is organized in Figure 4.

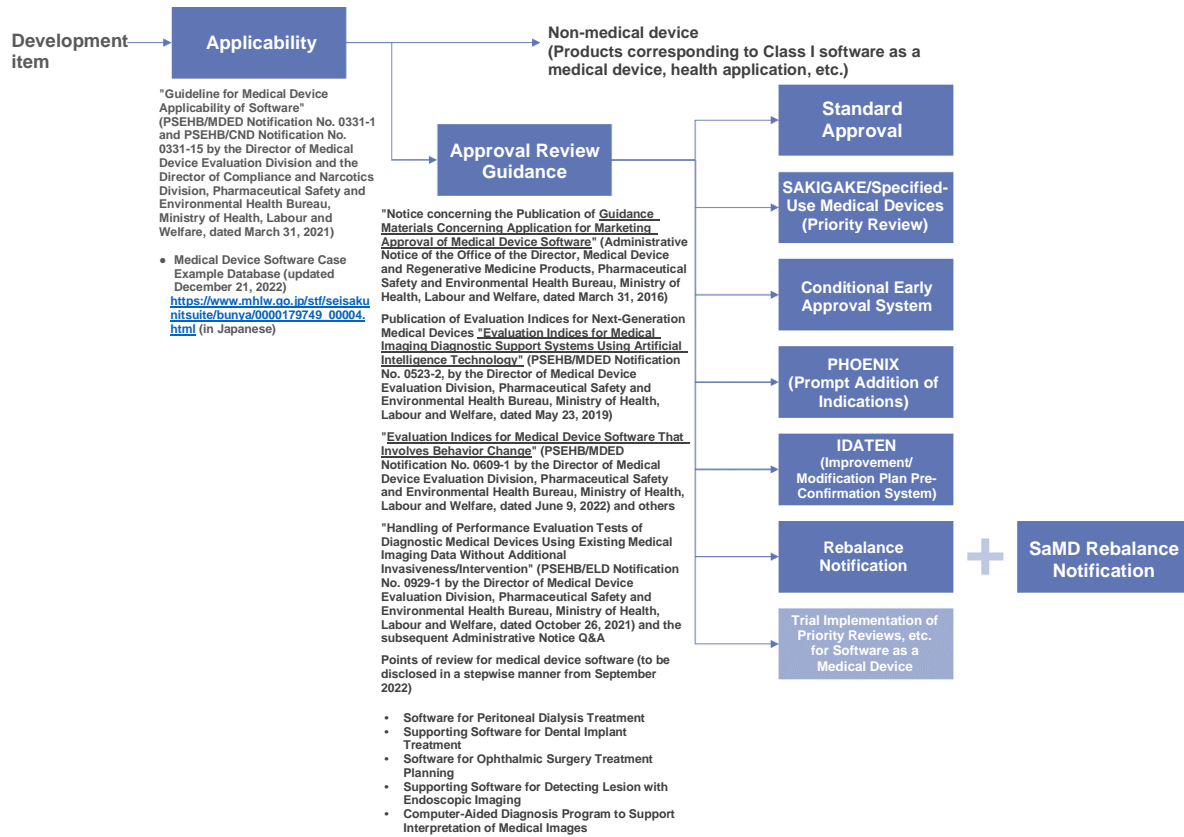


Figure 4. Options for Marketing Approval Applications in the Current System

2.3.1. Trial Implementation of Priority Reviews, Etc. for Software as a Medical Device

Software as a medical device is rarely the subject of the pioneering medical device designation system due to its characteristics. For example, many disease treatment software products target multifactorial diseases and do not meet the requirements of the existing pioneering medical device designation system in terms of the seriousness of the disease. In addition, disease diagnosis software may expect the improvement of the quality of diagnosis by non-specialists, which poses an issue of difficulty in evaluating the efficacy in relation to the designation requirements for efficacy compared with existing diagnostic methods. Based on these facts, the Ministry of Health, Labour and Welfare issued a notification "Trial Implementation of Priority Reviews, Etc. For Software as a Medical Device" (PSEHB/MDED Notification No. 0902-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated September 2, 2022). Subsequently, the Ministry of Health, Labour and Welfare issued a notification "Trial Implementation of Priority Reviews, Etc. for Software as a Medical Device (2nd)" (PSEHB/MDED Notification No. 0630-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated June 30, 2023).

These notifications specify the requirements for designation according to the characteristics of the software as a medical device while limiting the time frame. Then, the proposed designation product will be publicized¹⁵ if public offering, hearing, preliminary review, evaluation by PMDA, and deliberation/approval at the Pharmaceutical Affairs and Food Sanitation Council are completed. When the product is designated, actions including priority consultations, priority reviews, prior assessments, and concierge service will be taken with the target total review period of 6 months.

2.3.2. Designation System for Specified-Use Medical Devices

A specified-use medical device is designated by the Minister of Health, Labour and Welfare based on the opinion of the Pharmaceutical Affairs Council as a product that meets the conditions such as that the demand for the intended use is significantly unsatisfied and that the product is of particularly high medical needs based on Article 77-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

The purpose of this system is to contribute to the promotion of research and development of medical devices for which medical needs are significantly unsatisfied such as unestablished dosage and administration for children, and products which meet all of the following designation requirements may qualify.

(1) Designation Requirement 1: Target disease

Products satisfying any of the following:

- a Products that are to be used for diagnosis, treatment, or prevention of diseases in children and intended to obtain approval under Article 23-2-5 or Article 23-2-17 of the

¹⁵ In response to the results of deliberation by the Software as a Medical Device Subcommittee, the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare designated three products for the first meeting and three products for the second meeting.

Act

- b Products that have already been approved under Article 23-2-5 or Article 23-2-17 of the Act and are to be used for diagnosis, treatment, or prevention of diseases in children by changing the shape, structure, principle, or use method.

(2) Designation Requirement 2: Sufficiency of demand for the intended use

Products with significantly unsatisfied demand for the intended use and fall under any of the following:

- a No available existing therapeutic, prophylactic, or diagnostic method
- b More useful therapeutic, prophylactic, or diagnostic method is required than existing treatment from the viewpoint of efficacy, safety, or physical or mental burden on patients

(3) Designation Requirement 3: Particularly excellent value for the intended use

Products meeting both of the following criteria.

- a Products used supportively for very serious indication or diseases
- b Products established as a standard therapy in international guidelines, or those for which strong evidence has been obtained from randomized controlled studies.

2.3.3. Conditional Approval System for Medical Devices, Etc. (Including Expedited Addition of Indications)

Innovative medical devices for diseases which have a significant impact on life and do not have any effective existing therapies, are associated with considerable difficulty in collecting clinical data for approval application, such as prolonged clinical development due to the limited number of patients and substantial time required for the conduct of the clinical trial. Therefore, the "conditional approval system for medical devices, etc." in Article 23-2-5, Paragraph 1 or Paragraph 15 of the Pharmaceuticals and Medical Devices Act can be applied with conditions pursuant to the provisions of Paragraph 12 of the same article.

In "Handling of Conditional Approval of Medical Devices and In Vitro Diagnostics" (PSEHB/MDED Notification No. 0831-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020), the designation requirements are defined as medical devices that meet all of the requirements shown in the following (1) or (2).

(1) Type 1

- a. The target must be a disease that has a significant impact on life or a disease whose progression is irreversible and has a substantial impact on daily living.
- b. There is no available existing therapeutic, prophylactic, or diagnostic method, or markedly higher efficacy or safety than existing therapies is expected.
- c. The applicant can present appropriate clinical data for certain evaluations.
- d. The applicant can reasonably explain that there is considerable difficulty in

conducting a new clinical study or clinical performance study.

- e. The applicant can prepare proper use standards in close cooperation with related academic societies and concretely present a plan for collection and evaluation of post-marketing data.

(2) Type 2

- a. Medical devices or in vitro diagnostics that are intended to affect the structure or function of the human body by ablation or other physical functions and that are considered to be of particularly high medical need.
- b. The applicant can present appropriate clinical data with a certain level of extrapolability in order to evaluate the efficacy and safety in the range that has not been directly assessed by existing clinical data.
- c. The applicant can reasonably explain that the product's proper use can be ensured without conducting a new clinical study or clinical performance study.
- d. The applicant can prepare proper use standards in close cooperation with related academic societies and concretely present a plan for collection and evaluation of post-marketing data.

2.3.4. Improvement Design within Approval for Timely Evaluation and Notice (IDATEN)

This is a system to approve the modification plan itself for medical devices that are expected to be improved in the future according to the characteristics of them. For medical devices approved under Article 23-2-5, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, the provisions of Article 23-2-10-2 of the Act (including the case of application *mutatis mutandis* under Article 23-2-19 of the Act,) specify that predetermined confirmations are made.¹⁶ for the change plan for the intended use or indications, shape, structure, principle, raw materials, specifications for performance and safety, use method, storage method, shelf life, and manufacturing method of the medical device if an application is made by the person who intends to make a change plan of the medical device and implement it or have the designated marketing authorization holder do it.

When requesting a change plan confirmation, the applicant needs to apply for a PMDA pre-development consultation for medical devices and receive advice in advance on the change plan to be submitted.

Descriptions in the application form for change plan confirmation for software as a medical device should be prepared referring to related notifications such as the IDATEN Fundamental Notification, Administrative Notice for Description Examples (IDATEN Edition), and Questions and Answers (Q&A).

¹⁶According to the PMDA's self-evaluation of operating performance for FY 2021, two applications for change plan confirmation for software as a medical device were received in FY 2021, and one investigation was completed within the fiscal year. <https://www.pmda.go.jp/files/000248353.pdf>

2.3.5. Rebalance Notification

*Excerpted only from approvals based on "3. Consultation on Diagnostic Devices That Measure Physiological Parameters That May Serve as Reference Information for Diagnosis" of Rebalance Notification

Although some physiological parameters or numerical values obtained by computing them can be used as reference information for diagnosis, the relationship of them with clinical symptoms or pathological conditions has not been widely recognized. These parameters are not commonly expected to be used in medical practice at present, and we cannot say that their clinical significance and medical judgment criteria have been sufficiently established.

When developing a medical device that measures and presents such physiological parameters, the applicant may submit an application for approval only for the intended use or indications that can be shown by the past clinical results or study results on mechanical performance (measurement performance) even if the clinical significance as the final target has not been established yet.

In addition, an expected development strategy is one in which an application for approval of partial change is submitted as needed after clinical evidence is established based on experiences of use in clinical practice after approval (Figure 5).

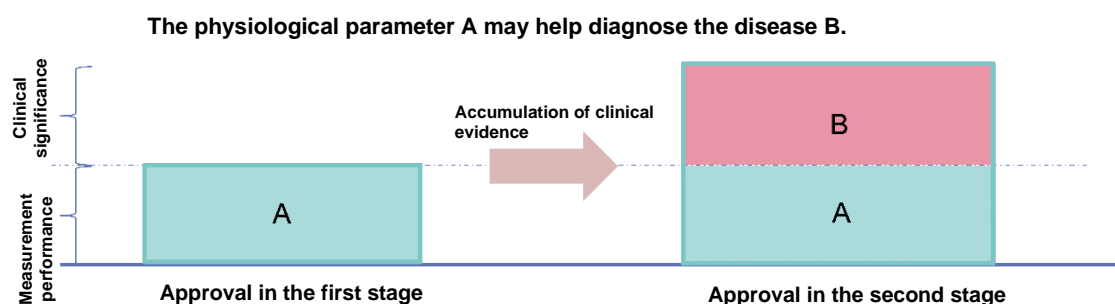


Figure 5. Conceptual Diagram of Development Strategy Based on Rebalance Notification

According to the Rebalance Notification, the applicable medical device is a device that measures physiological functions of a living body (excluding those related to sample testing), meets the following requirements, and is to be developed to support diagnosis.

- (1) An active monitoring medical device to perform noninvasive measurement of physiological indices shown as biological signals (e.g., so-called devices for testing biological physical phenomena, devices for testing bioelectric phenomena, devices for monitoring biological phenomena) that provides new indicators by computing information obtained from existing sensors of known measurement principles.
- (2) A product positioned as a medical device that separately provides one of several assessment criteria as reference information for diagnosis, although the final target clinical significance has not been established yet.
- (3) An erroneous test result may not have a significant impact on human life or health.

2.4. Principles for a New Regulatory Approval System for Further Acceleration of Launching

Software as a medical device is generally less invasive than conventional tangible medical devices and is less likely to cause major safety issues. In addition, this type of product is modified or improved for problems recognized with its use in clinical practice by frequent and diverse methods, making it easy to continuously improve the performance. Therefore, the software as a medical device product is expected to be introduced to the market as early as possible after the start of its development. Moreover, since the promotion of practical use of software as a medical device is expected to contribute to medical and welfare service reform including doctors' work style reform, there are many new entries in this field from other industries including start-ups, pharmaceutical companies, and other IT companies as well as many development programs led by academia compared with conventional tangible medical devices. Also, many software as a medical device product will be developed for use in the general living environment not limited to the conventional medical institutions. Therefore, it has been expected to clarify the principles on the regulatory approval system according to the characteristics of software as a medical device for further acceleration of launching.

"Interim Report on Promotion of Regulatory Reform (Council for Promotion of Regulatory Reform)" dated December 22, 2022 states as follows: *"Given the need to enable the early use of SaMD in clinical practice, we will advance the discussion while aiming to introduce a two-step approval system for SaMD (including the case where this is addressed by issuing a new SaMD Rebalance Notification). In the discussion, the first-stage approval will be studied according to the difference in the intended use and functions of the software as a medical device, such as sorting out the cases where the product can be evaluated in non-clinical studies or requires an exploratory clinical study and the scope of clinical significance labeled. For the approval in the second stage, the efficacy may be confirmed by utilizing clinical trials as well as real-world data."* The statement requires clarification of the principles that allow early introduction of software as a medical device to clinical practice after the start of its development.

In general, approval reviews for medical devices include discussions of data obtained from non-clinical and clinical studies, consideration for taking measures for risks, evaluation of the efficacy and safety as a medical device, and confirmation that there is an acceptable balance between the risks and benefits. On the other hand, it may take a long time to confirm the efficacy and safety in clinical studies. In addition, it is also considered that software as a medical device is unlikely to cause major safety problems. As a result, the evaluation in a limited number of subjects or medical institutions in clinical trials alone cannot completely clarify defects or adverse events when the device is used in many patients in various post-marketing clinical settings.

Therefore, on the premise that the safety is ensured, there is a possibility of a development strategy that establishes clinical significance by promoting the early launch based on the regulatory approval limited to a range for which a certain level of efficacy has been confirmed with probability from the data submitted at the time of approval application and by continuing the development while evaluating the efficacy and safety through the use in clinical practice.

In so doing, the most important thing is risk management; it is necessary to identify hazards from the beginning of the development based on the use method that is assumed in the clinical setting (use method and purpose intended by the developer), to estimate and evaluate risks, and to plan the method, before the launch, to evaluate the residual risks and monitor the acceptability after considering the effect of risk control and taking risk control measures. The risk evaluation is "to assess whether the risk is at an acceptable level according to the risk analysis under the current social values" and is based on the general

understanding for the safety of software as a medical device. Therefore, taking account of the differences in methods and viewpoints of post-marketing risk management depending on the use status, target disease, users, and other factors of the software as a medical device, it should be considered to promote early practical use of the software as a medical device if the legal requirements for marketing approval are satisfied and the benefits are judged to outweigh the risks.

Therefore, if the software as a medical device meets the legal requirements for marketing approval by proper and adequate risk management, etc., the first-stage approval will be given within a range (range of effects or performance labeled) where a certain level of efficacy can be confirmed with probability from the evaluation data (see Figure 6). Then, the evaluation data on the efficacy and safety of this product under use in clinical practice will be collected by post-marketing clinical study data, the later-mentioned real-world data, etc., and the second-stage approval of changing¹⁷ the intended use or indications by application for approval of partial changes can be given at the time when clinical evaluation data to demonstrate the efficacy with clinical significance are obtained.¹⁸

¹⁷ For changes made on software as a medical device, also refer to "2.2.3. Change in Software as a Medical Device."

¹⁸ The definition of a medical device is as follows in Article 2, Paragraph 2 of the Pharmaceuticals and Medical Devices Act: "(ii) The term refers to items which are intended to be used for the diagnosis, treatment, or prevention of diseases in persons or animals and which are not medical appliances or instruments, etc. (referring to medical appliances or instruments, dental materials, medical supplies, sanitary goods, and software [referring to instructions given to a computer and built so as to obtain a certain result; hereinafter the same applies] and recording media on which software is recorded; hereinafter the same applies) (excluding quasi-drugs and regenerative medicine products)." In the situation where no clinical significance is found in the approval review for the first stage, the product is outside the scope of the Concept of Two-Step Approval given the definition of a medical device in the Pharmaceuticals and Medical Devices Act. In other words, since software corresponding to Class I is excluded from the subject of medical device regulations, the Concept of Two-Step Approval applies to a software as a medical device product only when it can be approved as a Class II or higher product at the time of the first-stage approval.

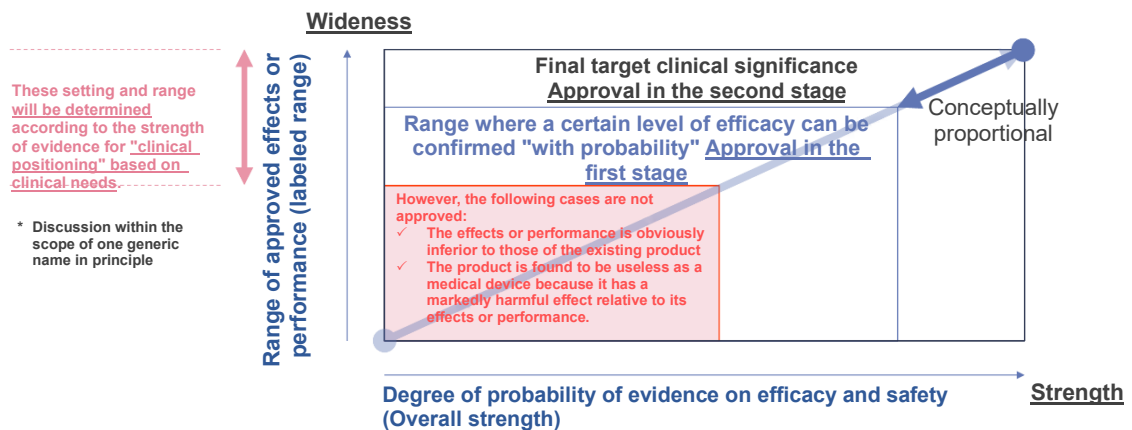


Figure 6. Conceptual Diagram of First-Stage Approval: Establishment of Effects or Performance According to the Strength of Evidence

However, with respect to the clinical evaluation plan necessary to obtain the second-stage approval, the applicant needs to advance the exchange of opinions with reviewers using PMDA's pre-development consultations before application for the first-stage approval. In particular, if the applicant considers a development plan taking account of new NHI points, etc., it is recommended that the developer and PMDA agree on the validity of the clinical evaluation plan to confirm the clinical significance for obtaining the second-stage approval in parallel with the application for the first-stage approval. In the process, it would be beneficial to simultaneously conduct a regulatory development consultation handled by the PMDA and a medical insurance consultation handled by the Office of Medical Devices Policy, Policy Planning Division for Pharmaceutical Industry Promotion and Medical Information Management, Health Policy Bureau, Ministry of Health, Labour and Welfare, which can be applied at the centralized consultation desk for SaMD in PMDA, and to exchange opinions among three parties including the marketing authorization holder.

In addition, for the range of clinical significance labeled at the time of the first-stage approval, i.e., the way of caution included in Precautions of the package insert, there are reference cases¹⁹ of approval that was limited to the range of intended use or indications that could be shown based on the previous clinical data and study results on functions or performance even though the final target clinical significance had not been established based on Rebalance Notification "3. Consultation on Diagnostic Devices That Measure Physiological Parameters That May Serve as Reference Information for Diagnosis." On the other hand, for the Concept of Two-Step Approval for software as a medical device, it is

¹⁹ In the cases of approval limited to the range of the intended use or indications that have been shown by clinical results or study results on mechanical performance to date, appropriate precautions have been provided by clearly stating that the approval is granted only to the range of the intended use or indications that have been shown by clinical results or study results on mechanical performance to date (so-called restriction on labeling). The example of such statements is the Precautions section related to the intended use or indications in the package insert stating as follows: "usefulness (clinical outcomes, etc.) of pain control based on information/indices presented by this product has not been evaluated," "Relationship between information on the ●●●● tomograph function presented by this device and lung function has not been established," "The relationship between information presented by ●●●● function and signs of exacerbation of heart failure has not been established," and "note that the clinical significance of biomarker values (●●●● biomarkers) output by this product has not been evaluated."

necessary to consider the ideal way of providing information²⁰, taking into account the facts that software as a medical device is considered to be less likely to cause safety problems and that continuous modifications and improvements are expected in performance or other specifications, while referring to the principles of Rebalance Notification.

In clinical evaluation required to obtain the second-stage approval, it is assumed²¹ that real-world data including registries may be used in addition to the results of post-marketing clinical studies.

Real-world data sources include data from medical records, health insurance claim data, data from disease registries, data from product registries for pharmaceuticals, medical devices, or regenerative medicine products, and data from other sources related to health status, including data from household devices and mobile devices²². Clinical evaluation data using real-world data do not fall under the category of clinical trials, and therefore the GCP Ministerial Ordinance for Medical Devices is not applied. However, the data need to be prepared in accordance with the data integrity standards for product applications as specified in Article 114-22 of the Enforcement Regulation, and therefore the integrity of the data must be properly ensured. Therefore, it is recommended that the applicant consult in advance about the integrity of real-world data by utilizing PMDA face-to-face consultations.

Concrete and extensive consideration of the relationship between real-world data and medical device regulations provides a rough classification²³ as shown in Table 5.

Based on the above discussion, the following measures are considered to promote development while properly managing the total product life cycle of software as a medical device and maintaining the balance between risks and benefits of the medical device.

²⁰ The example includes provision of information including the development status in terms of the performance and functions of software as a medical device, such as "●●●● function is provided based on the results of ●●●●." On the other hand, given the expectation that many first-stage approved products of software as a medical device will be introduced to the market in the future, it may be necessary to consider measures such as publication of the list of the first-stage approved medical devices based on the Concept of Two-Step Approval, so that users of the software as a medical device can select necessary products without confusion.

²¹ Although the utilization of real-world data has been actively considered as one of the data options used in regulatory applications, only a few cases employed real-world data for regulatory applications and these cases were rare disease cases or had difficulty in conducting clinical studies from an ethical standpoint. Therefore, it is important as a practical launch strategy to consider a development strategy in consideration of the possibility of the use of collectable real-world data in regulatory applications and the feasibility of clinical studies. Cooperation activities of industry, academia, and government are expected to promote the continuous use of real-world data.

²² From Registry Fundamental Notification

²³ Prepared taking into account the discussion by the study group based on the Utilization of Medical Real-World Data: Drug Discovery Technology Survey Report (Japan Health Sciences Foundation) Part 2, 2018.

Table 5. Types of Real-World Data and Viewpoints of Medical Device Regulations

Type	Description	Example	Viewpoint of medical device regulations
"Medical records, health insurance claims, etc." accumulated at each medical institution	The information on medical practice, results, insurance payment, etc. under routine medical care at each medical institution was recorded.	Electronic medical charts and health insurance claim information based on medical institutions, DPC DB, MID-NET, private DB (RWD, JMDC, etc.), health insurance claim DB of dispensing pharmacies outside the hospital	<ul style="list-style-type: none"> • Secondary use of data that are routinely obtained/accumulated at multiple institutions providing usual medical care. • As clinical evaluation data for regulatory approval, 0929 Notification may be used.
"Disease registry" accumulated by disease	DB of registered patients by disease, DB accumulated for disease cohort studies (patient registry/disease registration system)	SCRUM-Japan, muscular dystrophy Remudy, amyotrophic lateral sclerosis JaCALS, DB of designated intractable disease patients, DB of pediatric patients with chronic specific diseases, motor disorder registry JOANR, long-term prognosis registry for patients with deferral of coronary intervention based on fractional flow reserve J-CONFIRM	<ul style="list-style-type: none"> • A data collection system created for a specific purpose, and secondary use of data obtained/accumulated based on the rules established at the time of building the registry. • When a registry is used as clinical evaluation data for regulatory approval: <ul style="list-style-type: none"> [1] A registry to be created from now should be handled based on the Registry Fundamental Notification and Registry Data Reliability Notification, which will lead to the utilization of data taking account of regulatory actions. [2] On the other hand, when using the data obtained from a registry created before the issuance of these notifications, data integrity is a key point, and therefore PMDA consultations should be made individually in advance.
"Product registry" accumulated when a specific medical device is used	DB accumulated for a use-results survey in all patients as a condition for approval according to the Pharmaceuticals and Medical Devices Act	J-MACS registry, TAVI registry (since the TAVI registry uses and the Japan Cardiovascular Surgery Database (JACVSD), which was already established mainly by the Japanese Society for Cardiovascular Surgery, it can be said that the registry is a "disease registry" as a major classification)	<ul style="list-style-type: none"> • Data obtained from approved/certified medical devices. • For utilization of the data as clinical evaluation data for regulatory approval, 0929 Notification may be used on the premise that the data are within the range predetermined for approved/certified medical devices.
"Medical device data" that record data accumulated in medical devices	DB that records information obtained from products approved/certified as medical devices	Image information such as Picture Archiving and Communication System (PACS) and image workstations, cardiovascular information (blood pressure, pulse rate, heart sound, electrocardiogram, and electroencephalogram), metabolic information (blood glucose level and HbA1c), etc.	<ul style="list-style-type: none"> • Data obtained from approved/certified medical devices. • For utilization of the data as clinical evaluation data for regulatory approval, 0929 Notification may be used on the premise that the data are within the range predetermined for approved/certified medical devices.
"Data obtained from mobile health devices" that record life data	DB that records information obtained from non-medical mobile health devices	Behavioral information (number of steps, walking distance, amount of exercise, and sleep time), camera image information, voice information, etc.	<ul style="list-style-type: none"> • Data obtained from non-medical devices. • When using the data as information related to clinical evaluation data in regulatory approval, the adequacy of accuracy control, etc. for the non-medical device is judged (presence or absence of an accessory function with ensured reliability).
Data collected and provided by public institutions	DB that records information provided by public institutions	Weather observation data, global environment and climate observation and analysis data, marine observation and analysis data, etc.	<ul style="list-style-type: none"> • Secondary use of data provided by public institutions. • When using the data as information related to clinical evaluation data in regulatory approval, the validity of methods²⁴ for information collection and the management system of such information conducted by the public institution is judged (the range of publicly guaranteed accuracy and others).

²⁴ For example, the meteorological observation data provided by the Japan Meteorological Agency have the Meteorological Observation Statistics Guideline. The observation and quality control of the observed values are performed based on this guideline. This guideline is not only the "technical standards for statistics on meteorological observation performed by the Japan Meteorological Agency", but also positioned as a "manual for conducting various statistics using basic weather observation statistics materials provided by the Japan Meteorological Agency", and may serve as a rationale for the reliability of data.

2.4.1. Concept of Two-Step Approval for Software as a Medical Device for Disease Diagnosis

We expect the development of software as a medical device that: (1) calculates physiological parameters, risk scores, and features from various test results, all of which are considered to be a type of reference information for diagnosis or prognosis prediction but whose clinical significance or medical assessment criteria have not been established because the relationship between the clinical symptoms or pathology and the physiological condition has not been widely recognized; (2) indicates a region of interest, etc. from medical image data such as CT; or (3) predicts the patient exacerbation risk by the analysis function such as an active monitoring medical device for physiological indicators related to biological signals.

Because clinical significance of such software as a medical device may become clear after it is widely used, one possible development strategy is as follows: to obtain the first-stage approval limited to the range of the intended use or indications that can be shown by study data of non-clinical studies and mechanical performance (measurement performance, detection performance, and computing performance) after summarizing the clinical results and explaining the clinical significance of the calculated physiological or other parameters after consultation with PMDA even at a stage when the final target clinical significance has not been established; and then to obtain the second-stage approval by making an approval application for partial change where necessary after the clinical evidence (e.g., post-marketing clinical studies, real-world data) is established in the post-marketing setting based on the experience of use in clinical practice (Figure 5).

Specifically, when considering a development strategy based on the Concept of Two-Step Approval for software as a medical device that meets the following three conditions, it is considered useful for the applicant to exchange opinions with the reviewer in advance using the PMDA pre-development consultation.

- [1] Software as a medical device to calculate physiological parameters, etc. from an active medical device for physiological indicators related to biological signals (e.g., a device for testing biological physical phenomena, a device for testing biological electrical phenomena, a device for monitoring biological phenomena, an image diagnosis device), etc., medical devices for non-invasive measurement and imaging, etc., internal or external sensors (hereinafter referred to as the "general-purpose sensors, etc.") of a web camera, etc. of a general-purpose computer including a mobile information terminal such as smartphones, and various test information, etc.
- [2] Products that are positioned as software as a medical device that provides one of several assessment criteria as reference information for diagnosis.
- [3] No safety concern affecting the original diagnostic results is expected even if the information in question is referred to.

On the other hand, in the following cases, for example, more detailed information is expected clinically, and therefore the applicant should note that it is not always appropriate to employ the Concept of Two-Step Approval.

- Fields in which the results of test/diagnosis directly and significantly affect medical decisions in treatment (e.g., treatment policy for cancer, initial response policy in emergency medical care)
- Fields where new information is being provided on a daily basis and is evolving, such as genetic testing
- Fields where the clinical significance and medical judgment criteria have been

established for the information provided by the software as a medical device such as pulmonary nodules and polyps (e.g., there are similar approved products)

- A medical device or software as a medical device similar to the proposed product has obtained second-stage approval and is used in clinical practice.

For software as a medical device for diagnosis, there are already many cases where approval has been obtained by conducting evaluations of clinical usefulness and performance with Notification 0929, etc., not based on clinical trials. Therefore, early market introduction may be possible without applying the Concept of Two-Step Approval, and it is considered useful for the applicant to exchange opinions with PMDA from the development stage.

2.4.2. Concept of Two-Step Approval for Software as a Medical Device for Disease Treatment

For software as a medical device that has a performance or function to provide information for assisting or supporting the treatment of a disease but whose clinical evidence as a treatment has not been established, the applicant needs to give an evidence-based explanation of the clinical significance of the software as a medical device as a treatment.

On the other hand, there are cases where the feasibility of a clinical study is low due to problems of subject recruitment in a Japanese clinical study and a required long evaluation period in the cases of software as a medical device for disease treatment related to multifactorial diseases in which various factors such as genetics and lifestyle are combined or related to the psychiatric disease area, pain, and functional syndrome, in which the primary endpoint for efficacy evaluation employs the patient's subjective measure. Some of these software as a medical device product do not have sufficient clinical evidence or clinical significance as a treatment for a disease. However, there are also some other products that show alleviation of specific symptoms of the disease or improvement of the condition, can be provided in a way that ensures a certain level of quality by assisting or supporting the treatment administered by a physician, or are expected to be useful for patients and clinical practice.

For such software as a medical device, one possible development strategy is as follows: to obtain the first-stage approval, after consultation with the PMDA, for the intended use or indications limited to the range in which a certain level of efficacy can be confirmed with probability based on the results of exploratory clinical studies for specific symptom relief or condition improvement, in addition to the study results of performance evaluation, even if the final target clinical significance has not yet been established; and then to obtain the second-stage approval by making an approval application for partial changes as necessary after the clinical evidence (e.g., post-marketing clinical studies, real-world data) is established in the post-marketing setting based on the experience of use in clinical practice (Figure 7).

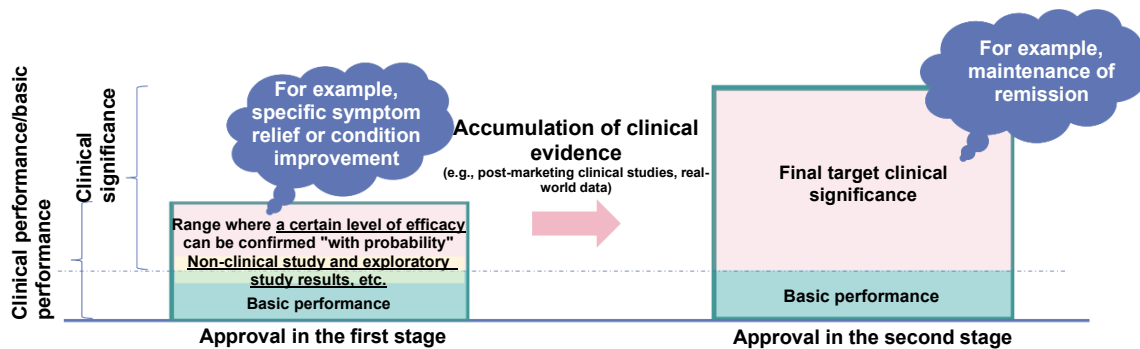


Figure 7. Conceptual Diagram of Development Strategy Based on the Concept of Two-Step Approval of Software as a Medical Device for Disease Treatment

Specifically, when considering a development strategy based on the Concept of Two-Step Approval for software as a medical device that meets the following two conditions, it is considered useful for the applicant to exchange opinions with the reviewer in advance using the PMDA pre-development consultation.

- [1] A certain level of efficacy can be confirmed with probability, such as relief of a specific symptom or improvement of a specific condition shown by non-clinical and exploratory clinical study results, although the clinical significance as a treatment method for the final target disease has not been established yet.
- [2] Safety concerns that affect existing treatment, etc. are not expected when the software as a medical device assists or supports treatment by physicians based on information presented by the software.

In addition, it should be noted that the above Concept of Two-Step Approval is not always appropriate because more detailed information is expected clinically if a medical device or software as a medical device similar to the proposed product has obtained second-stage approval and is used in clinical practice.

On the other hand, since there have been not many approvals on software as a medical device for disease treatment at present, it is assumed that even for disease areas and software as a medical device to which the Concept of Two-Step Approval does not apply, the characteristics and functions of desired software as a medical device may change according to the future treatment policy and the status of introduction of treatment methods in clinical practice. Therefore, the applicant should consider flexibly addressing the Concept of Two-Step Approval.

2.4.3. Concept of Two-Step Approval for Software as a Medical Device for Disease Prevention

There is the definition of the category in the appended table 1 of Order for Enforcement as follows: "3 software for disease prevention (excluding those that are unlikely to affect human life or health even if an adverse reaction or malfunction occurs; hereinafter the same applies in the following paragraph, item (iii))." At present, however, there have been no approvals with the term name or category name, yielding no results enough to organize the Concept of Two-Step Approval. Therefore, it is expected that the concept will be organized according to the future development and approval results.

In preventive medicine, the concept of prevention is classified into primary prevention, secondary prevention, and tertiary prevention. In general, primary prevention refers to efforts of treatment and guidance at the premorbid stage, such as health promotion (including health education) and prevention of onset by vaccination. Secondary prevention refers to efforts such as prevention of aggravation by early detection and early treatment. Tertiary prevention refers to efforts such as promoting return to society by providing rehabilitation to maintain and restore functions and prevention of recurrence by health guidance in the course of treatment.

Accordingly, many products of software as a medical device that contribute to secondary or tertiary preventions can use the evaluation principles for software as a medical device for diagnosis or treatment. It is considered that the actual application will be handled taking into account the term names of software as a medical device for diagnosis or treatment.

On the other hand, software as a medical device that contributes to primary prevention including health promotion may fall under the following categories, which are not subject to the Pharmaceuticals and Medical Devices Act²⁵ because the software does not meet the definition of a medical device in the Applicability Guideline. "(3) Software for users (patients or healthy persons) to access their medical and health information: [1] Software that stores, manages, and displays personal health records; and [2] Software not for medical or health purposes, such as training management for sports" and "(4) Software that is considered to have a low risk of affecting life and health: [1] Software that performs processing equivalent to a tangible general medical device (Class I)." Friends of WHO JAPAN introduces the definition of health as follows: *"The preamble of WHO Charter adopted in 1947 defines 'health' as follows: 'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.' The definition of health is still widely used throughout the world."* Given this definition of health, it may be extremely difficult at present to have a unified view among the parties concerned on how to define the clinical significance finally targeted by the software as a medical device.

²⁵Refer to Applicability Guideline for details. In addition to this notification, The "Medical Device Software Case Example Database (in Japanese)" is published on the website of Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000179749_00004.html), which is updated as needed for clarification/elaboration regarding applicability decision of software as a medical device.

3. Conclusion

In recent years, improvement in information processing technology such as AI has increased the value of information provided by software as a medical device, has led to the development of software as a medical device to transform behaviors, expressed as the digital doctor, or to display disease signs or triage, and has resulted in the appearance of wearable products that can be used outside medical institutions. Due to the widening range of software as a medical device and current and future issues on medical resources in Japan, their early practical use and launch are expected.

In this situation, this guidance is intended for earlier launch of software as a medical device and summarizes our best measures to be taken at this point that are prepared in discussion with related parties in industry, academia, and government. In other words, this is a product implemented as guidelines made from both the development experience and approval review experience to date, so that everyone can share and use the empirical knowledge for early launch of software as a medical device.

On the other hand, although the number of software as a medical device has been increasing year by year, there are still only a few products qualified as a new medical device, and most products have been approved within the review framework of improved medical devices or generic medical devices. In addition, there have been a sufficient number of approvals in the existing approval system. These two facts succinctly indicate that approval reviews are performed flexibly depending on the positioning of development items even for software as a medical device. This fact was fully considered in the preparation of this guidance. That is, for the preparation of this guidance, discussions were advanced from the viewpoint of clarifying the Concept of Two-Step Approval for software as a medical device, but these discussions also clarified the scope of software as a medical device for which the applicant can effectively use the existing approval system. The development strategy based on the Concept of Two-Step Approval is likely to accelerate the launch of the product itself. However, it is assumed that certain restrictions will be imposed on the labeling at the time of marketing and insurance strategy. Therefore, not all software as a medical device need to be launched through the Concept of Two-Step Approval, and it is desirable for each developer to consider the launch strategy while understanding this distinction and merits and demerits of the conventional system.

Given the diversity of software as a medical device, there is a limitation in a general approach. As future developments, increases in individual next-generation evaluation indices and review points of medical device software are expected. For the time being, it is anticipated that individual review points will increase. When individual review points and other information are accumulated, it is strongly expected that this guidance will be reviewed at a certain interval and that the environment will be further improved so that software as a medical device can be continuously created.

Main Related Notifications, etc.

- "Handling of Medical Device Software" (PFSB/MDRMPED Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29 by the Director of the Medical Device and Regenerative Medicine Product Evaluation, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, the Director of the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, and the Director of the Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014)
- "Questions & Answers About Handling of Medical Device Software" (Office of the Director, Medical Device and Regenerative Medicine Products, Safety Division, and Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 25, 2014)
- "Questions & Answers About Handling of Medical Device Software (Part 2)" (Office of the Director, Medical Device and Regenerative Medicine Products and Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 30, 2015)
- "Partial Revision of Guideline for Medical Device Applicability of Software" (PSEHB/MDED Notification No. 0331-1 and PSEHB/CND Notification No. 0331-4 by the Director of Medical Device Evaluation Division and the Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2023)
- "Cases for Judging the Medical Device Applicability of Software" (Administrative Notice of the Medical Device Evaluation Division and the Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2023)
- "Description Examples of Application Forms and Submission Data for Marketing Approval (Certification) of Medical Device Software" (Administrative Notice of the Office of the Director, Medical Device and Regenerative Medicine Products, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated February 10, 2015)
- "Notice Concerning the Publication of Guidance Materials Concerning Application for Marketing Approval of Medical Device Software" (Administrative Notice of the Office of the Director, Medical Device and Regenerative Medicine Products, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2016)
- "Handling of Minor Change Procedures in Association with Partial Change of Medical Device Software" (PSEHB/MDED Notification No. 1020-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated October 20, 2017)
- "Handling of Application for Change Plan Confirmation for Medical Devices" (PSEHB/MDED Notification No. 0831-14 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020)
- "Description Examples of Application Forms and Submission Data for Application for Change Plan Confirmation for Software as a Medical Device" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of

Health, Labour and Welfare, dated December 22, 2023)

- "Questions and Answers (Q&A) on Application for Change Plan Confirmation for Medical Devices, Medical Devices Using Artificial Intelligence-Related Technology, and Software as a Medical Device" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated December 22, 2023)
- "Handling of Performance Evaluation Tests of Diagnostic Medical Devices Using Existing Medical Imaging Data Without Additional Invasiveness/Intervention" (PSEHB/MDED Notification No. 0929-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated September 29, 2021)
- "Questions and Answers (Q&A) on Handling of Performance Evaluation Tests of Diagnostic Medical Devices Using Existing Medical Imaging Data Without Additional Invasiveness/Intervention" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated December 8, 2022).
- "Points to Consider for Smooth Implementation of Document-Based Compliance Inspection for Medical Devices (Non-clinical Studies)" (Administrative Notice of the Office of Non-clinical and Clinical Compliance, Pharmaceuticals and Medical Devices Agency, dated February 9, 2018).
- "Publication of Evaluation Indices for Next-Generation Medical Devices: Attachment 3 Software for Blood Flow Simulation" (PSEHB/MDED Notification No. 0523-2 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated May 23, 2019)
- "Publication of Evaluation Indices for Next-Generation Medical Devices: Attachment 4 Evaluation Indices for Medical Imaging Diagnostic Support Systems Using Artificial Intelligence Technology" (PSEHB/MDED Notification No. 0523-2, by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated May 23, 2019)
- "Publication of Next-Generation Evaluation Indices for Medical Devices: Attachment 2 Evaluation Indices for Medical Device Software That Involves Behavior Change" (PSEHB/MDED Notification No. 0609-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated June 9, 2022)
- "Handling on the Scope of Situations Where "Documents Related to Clinical Study Results" Is Necessary on Medical Devices (Operations Based on Measures Through Pre-and Post-Marketing Phases)" (PSEHB/MDED Notification No. 1117-1 and PSEHB/PSD Notification No. 1117-1 by the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017)
- "Release of Clinical Trial Guidance to Facilitate the Speedy and Accurate Approval and Development of Medical Devices" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 17, 2017)
- "Handling of Medical Devices for Physicians Concerning Off-label Use" (HPB/RDD Notification No. 0522001 and PFSB/ELD Notification No. 0522001, by the Director of Research and Development Division, Health Policy Bureau and by the Director of

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated May 22, 2006)

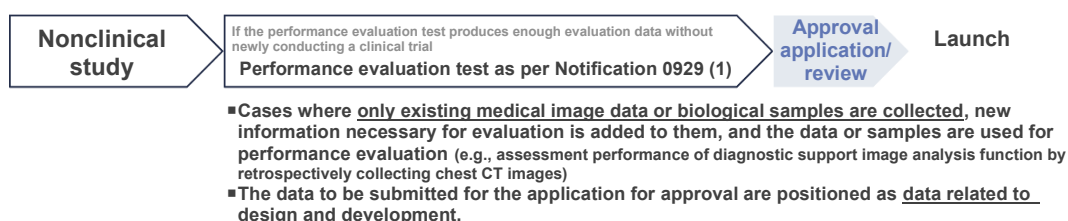
- "Basic principles on Utilization of Registry for Applications" (PSEHB/PED Notification No. 0323-1 and PSEHB/MDED Notification No. 0323-1, by the Director of Pharmaceutical Evaluation Division and the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2021)
- "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications" (PSEHB/PED Notification No. 0323-2 and PSEHB/MDED Notification No. 0323-2, by the Director of Pharmaceutical Evaluation Division and the Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2021)
- "Questions and Answers (Q&A) on Points to Consider for Ensuring the Reliability in Utilization of Data from Registry or Medical Information Database in Applications for Marketing Approval and Re-Examination for Regenerative Medical Products" (Administrative Notice of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 31, 2023)
- "Relationship Between the Use of Software to Support Diagnosis and Treatment Using Artificial Intelligence (AI) and the Provisions of Article 17 of the Medical Practitioners' Act" (HPB/MPD Notification No. 1219-1 by the Director of Medical Professions Division, Health Policy Bureau, Ministry of Health, Labour and Welfare, dated December 19, 2018)
- "Revision of Good Review Practice for Medical Devices" (Administrative Notice of the Office of Medical Devices I, Office of Medical Devices II, and Office of Medical Devices III, Pharmaceuticals and Medical Devices Agency, dated June 3, 2016)
- "Regulatory Science on AI-based Medical Devices and Systems" (AI Subcommittee, Science Board, December 27, 2017)
- "Subcommittee Report on Concept of Review of Medical Device Software Using Computer Simulation" (Subcommittee on Computer Simulation, Science Board, March 30, 2021)
- "Report on AI-based Software as a Medical Device (SaMD) " (Subcommittee on Software as a Medical Device Utilizing AI and Machine Learning, Science Board, August 28, 2023)
- "Review Points for Medical Device Software (SaMD) (in Japanese)" (<https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0047.html>)
- "Frequently Asked Questions for Software as a Medical device (in Japanese)" (<https://www.pmda.go.jp/files/000264780.pdf>)

Appendix 1-1: Case Examples of Development and Approval Processes of Software as a Medical Device for Disease Diagnosis

* The case examples provide general processes for development and approval referring to existing approval cases and do not apply to all products. Also, the examples do not include factors of the IDATEN change plan and exclude gene mutation analysis or similar software.

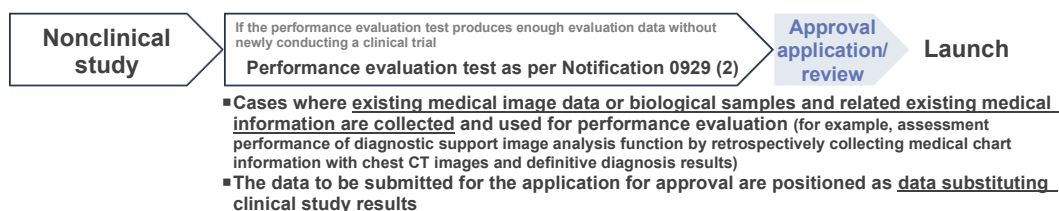
[Case 1] Improved medical device (without clinical data)

- Software for MR system workstations (Class II)
- Endoscopic diagnostic imaging support software for lesion detection (Class II)
- Software for endoscopic diagnostic imaging support for differential diagnosis of diseases (Class II), etc.



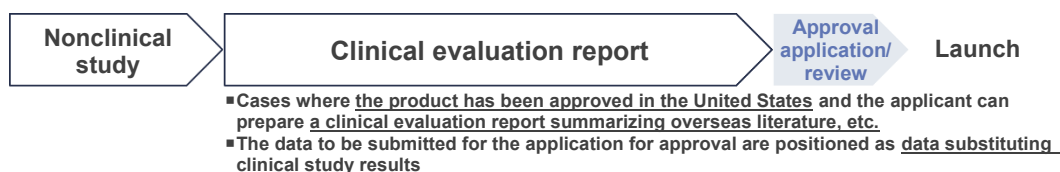
[Case 2] Improved medical device (with clinical data)

- Software for X-ray diagnostic imaging system workstations (Class II), etc.



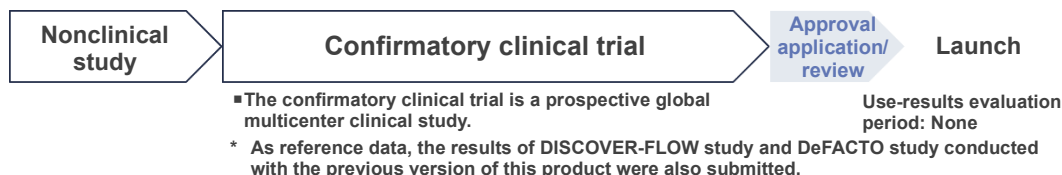
[Case 3] Improved medical device (with clinical data) *Overseas development

- Software for general-purpose diagnostic imaging system workstations (Class II)
- Home electrocardiograph software (Class II), etc.



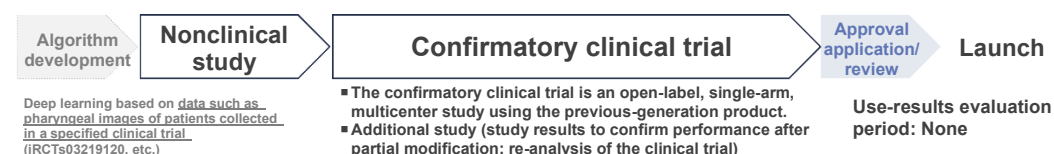
[Case 4] New medical device *Overseas development

- Hemodynamic analysis software (Class II)



[Case 5] New medical device *Development in Japan

- Software to support detection of disease characteristic findings for endoscopy (Class II)



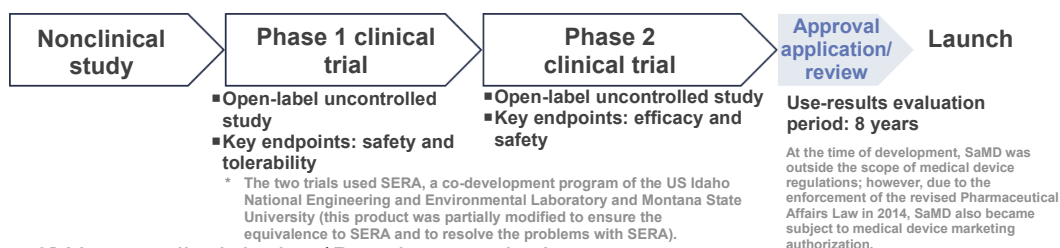
Appendix 1-2: Case Examples of Development and Approval Processes of Software as a Medical Device for Disease Treatment

* The case examples provide general processes for development and approval referring to existing approval cases and do not apply to all products. It also does not include factors of the IDATEN change plan.

[Case 1] New medical device *Development in Japan

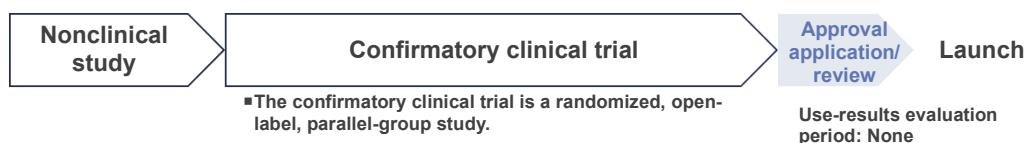
- Treatment planning software for boron neutron capture therapy (Class III)

*Software as a medical device used for calculating dose distributions for BNCT, a combination therapy of a boron agent and neutron irradiation (A drug marketing application was made for the combined boron agent at the same time, and a medical device marketing application had been made for neutron irradiation equipment for BNCT)



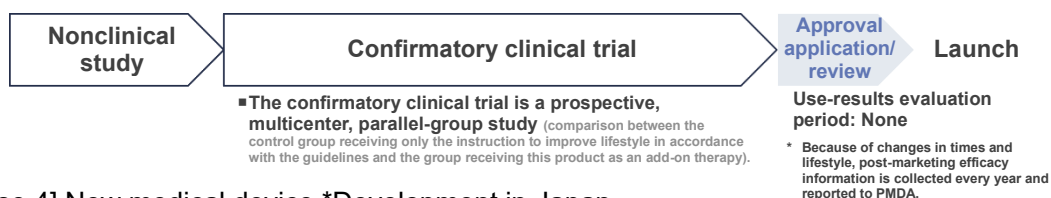
[Case 2] New medical device *Development in Japan

- System to aid smoking cessation treatment (Class II): With tangible objects



[Case 3] New medical device *Development in Japan

- Hypertension treatment support software (Class II)



[Case 4] New medical device *Development in Japan

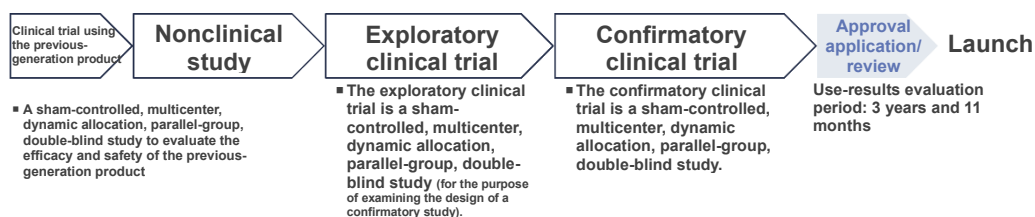
- Software to control general anesthetic drug administration (Class III)

*The biological information monitor and syringe pump used concomitantly were already certified or approved medical devices. The drugs are generic drugs of propofol, remifentanyl, and rocuronium, all of which have been approved as original drugs. The doses determined by this product are also within the range of dosage and administration of the original drugs.



[Case 5] New medical device *Development in Japan

- Sleep disorder software (Class II)



Appendix 2: Case Examples Related to This Guidance

- * The case examples were prepared to supplement Chapter 2 "Integrated Principles on Appropriate and Prompt Approval and Development of Software as a Medical Device" based on the discussion described in this guidance. These cases are shown as examples of the principle and do not apply to all products. The cases not described here may be handled differently according to future technical progress, development of non-clinical study methods, and accumulation of clinical data. It is also expected that a certain level of efficacy, etc. presented at the time of the first-stage approval may be subject to the second-stage approval owing to changes in treatment policies in medical practice in the future. Furthermore, the product under development may be handled differently from the case examples due to the product's degree of novelty. Therefore, it is useful for the applicant to consult PMDA where necessary, referring to "2.2. General Principles for Considering a Development Strategy Taking Into Account the Viewpoint of Approval Review" in this guidance and considering the Concept of Two-Step Approval.

[Case 1] Software for central monitor with analysis function, etc. (software as a medical device for disease diagnosis)

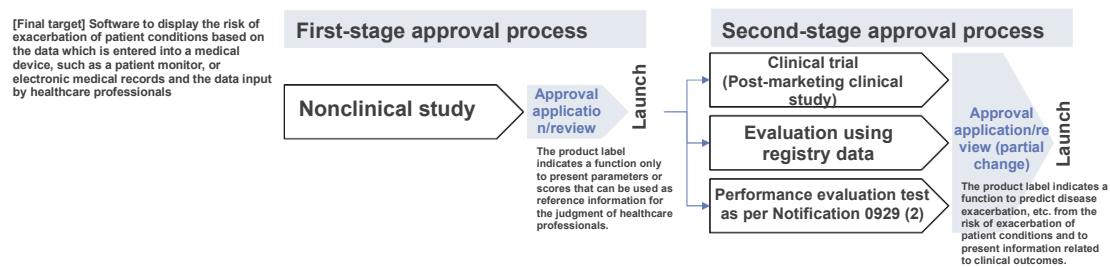
The product is software to collect and analyze clinical data obtained from a central monitor or medical information system connected to a network to assess/predict risks. It is possible to consider the first-stage approval if the product label indicates a function only to present parameters or scores that can be used as reference information for the judgment of healthcare professionals. Whether or not the product can help patients avoid disease exacerbation when risks are presented depends on the availability of established procedures according to the presented risks.

If the product label indicates a function to predict disease exacerbation, etc. from parameters or scores and to present information related to clinical outcomes, it is necessary to evaluate the relationship with patient prognosis, etc. in clinical studies. Therefore, it is possible to consider the second-stage approval by collecting relevant data after the first-stage approval and by using these post-marketing clinical study results.

[Case 2] Software to evaluate exacerbation of patient conditions, etc. (software as a medical device for disease diagnosis)

The product is software to display the risk of exacerbation of patient conditions based on the data which is entered into a medical device, such as a biological monitor, or electronic medical records and the data input by healthcare professionals. It is possible to consider the first-stage approval if the product label indicates a function only to present parameters or scores that can be used as reference information for the judgment of healthcare professionals. Whether or not the product can help patients avoid disease exacerbation when risks are presented depends on the availability of established procedures according to the presented risks.

If the product label indicates a function to predict disease exacerbation, etc. from the risk of exacerbation of patient conditions and to present information related to clinical outcomes, it is necessary to evaluate the relationship with patient prognosis, etc. in clinical studies. Therefore, it is possible to consider the second-stage approval by collecting relevant data after the first-stage approval and by using these post-marketing clinical study results.



Conceptual diagram of development and approval processes of software to evaluate exacerbation of patient conditions

[Case 3] Osteoporosis assessment software, etc. (software as a medical device for disease diagnosis)

For software to indicate the risk of osteoporosis in patients based on images such as X-ray images that have not been used for the diagnosis of osteoporosis so far, it is possible to consider standard approval by showing that the accuracy of diagnosis with the developed product is not inferior to that of the existing product based on the studies using existing medical care information in accordance with the Notification 0929, instead of the Concept of Two-Step Approval.

[Case 4] Software to aid diabetes treatment, etc. (software as a medical device for disease treatment)

Software that aims to encourage patients to change their behavior by inputting information and responding to the output displayed based on a unique algorithm and, for example, to improve blood glucose levels in patients with diabetes mellitus. If the result of an exploratory clinical trial to evaluate the relief/improvement of pathological symptoms derived from diabetes mellitus shows the relief/improvement of such symptoms, it is possible to consider the first-stage approval as software as a medical device to relieve/improve symptoms.

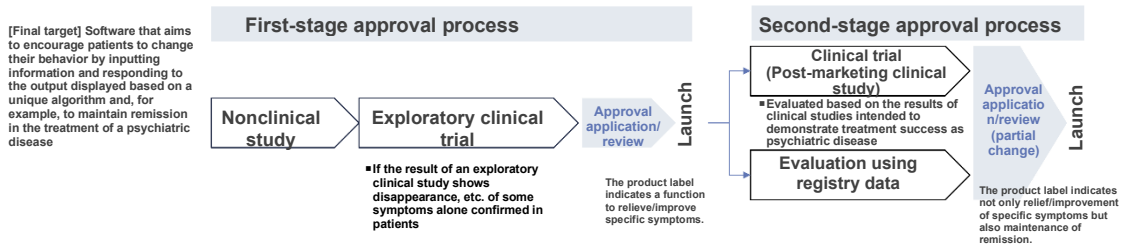
If the product label indicates not only relief/improvement of specific symptoms but also improvement of diabetes mellitus or long-term efficacy, evaluation should be conducted based on the results of clinical studies intended to demonstrate treatment success as diabetes mellitus. Therefore, it is possible to consider the second-stage approval by collecting related data after the first approval and by using these post-marketing clinical study results.

[Case 5] Software to aid psychiatric disease treatment, etc. (software as a medical device for disease treatment)

For the software that aims to encourage patients to change their behavior by inputting information and responding to the output displayed based on a unique algorithm and, for example, to maintain remission in the treatment of a psychiatric disease, it is possible to consider the first-stage approval as software as a medical device to relieve/improve symptoms if the result of an exploratory clinical study shows disappearance, etc. of some

symptoms alone confirmed in patients.

If the product label indicates not only relief/improvement of specific symptoms but also maintenance of remission, evaluation should be conducted based on the results of clinical studies intended to demonstrate treatment success as psychiatric disease. Therefore, it is possible to consider the second-stage approval by collecting related data after the first approval and by using these post-marketing clinical study results.



Conceptual diagram of development and approval processes of software to aid psychiatric disease treatment, etc.

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[FY 2023 Project to Review the Data Reliability, etc. in Regulatory Approval of Software as a Medical Device]

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