Guidance on the Review and Approval of Digital Therapeutics(DTx)

August 2020

MINISTRY OF FOOD AND DRUG SAFETY
National Institute
of Food and Drug Safety Evalution
Medical Device Evaluation Department

Revision History

Guidance on Review and Approval of Digital Therapeutics(DTx)

No. of Establishment/Amendment	Approval Date	Description
Guidance-1045-01	2020.08.27	Initial establishment

This guidance represents the position of Ministry of Food and Drug Safety or explains the scope and the criteria on the review and approval of digital therapeutics.

This guidance does not establish legally enforceable responsibilities. Please note that, despite some expressions contained herein (such as "shall (should)"), you are not required to comply with this guidance. In addition, this guidance has been prepared based on scientific and technical facts and statutes that are valid and effective as of August 26, 2020. The provisions in this guidance are subject to change depending on the revision of the relevant statutes or specific factual basis.

※ Guidance for Industry refers to the description of legislation or administrative rules offered to industry to aid their understanding or the proclamation of the stance of regulatory authority in relation to certain civil affairs (Article 2 of the Regulations on the Management of Guidelines, etc. of the Ministry of Food and Drug Safety)

Contact
Digital Health Devices Division, Medical Device Evaluation Department, National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety
Tel : +82-43-719-3982
Fax: +82-43-719-3940
email: digitalhealth@korea.kr

Table of Contents

I Overview

1. Background and Objective

Personalized medicine for patients has been trending along with the development of Information and Communications Technology (ICT), including big data and artificial intelligence.

Following this trend, the digital medical devices of today do more than detecting diseases, monitoring patients, and assisting clinical decision making. In this regard, Software as a Medical Device (SaMD) intended for prevention, control and treatment of disabilities and diseases is taking the spotlight.

Compared to conventional medicine, Digital Therapeutics (DTx) has a lower cost, shorter timescale to develop and various applicable technologies, including virtual/augmented reality and artificial intelligence.

In particular, the DTx products for treatment on behavior correction, chronic diseases, and collection and analysis of patient's data have been developed recently in clinical field. Therefore, in order to provide proactive and predictable regulations for the novel field, it is necessary to set forth definitions, criteria and the methods for review and approval of a DTx.

This guidance is based on the “Regulation on Medical Device Approval/Report/Review, Etc” of the Enforcement Regulation of the Medical Device Act (hereinafter referred to as "Regulation") and seeking to enhance transparency in applicant’s convenience and duties of

review and approval by representing the current scope, criteria, and the methods for review and approval of a DTx.

2. Scope

This guidance shall apply to the approval/certification of the manufacturing/import, review of technical documents, and approval of clinical trial protocols for a DTx that provide evidence-based therapeutic intervention to patients for preventing, managing, or treating medical disorders or diseases.

3. Definitions

A. Digital Therapeutics (DTx)

Software as a Medical Device (SaMD) that provides evidence-based therapeutic intervention to patients for prevention, control, or treatment of medical disorders and/or diseases.

※ The use of a DTx is for “patients” who require therapeutic intervention

B. Software as a Medical Device (SaMD)

Software intended to be used for one or more medical purposes without being part of a hardware medical device (IMDRF/SaMD WG/N10FINAL:2013).

※ For more information of this definition, please refer to the above document.

C. Real World Evidence (RWE)

Real World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of Real World Data (RWD).

D. Prospective Study

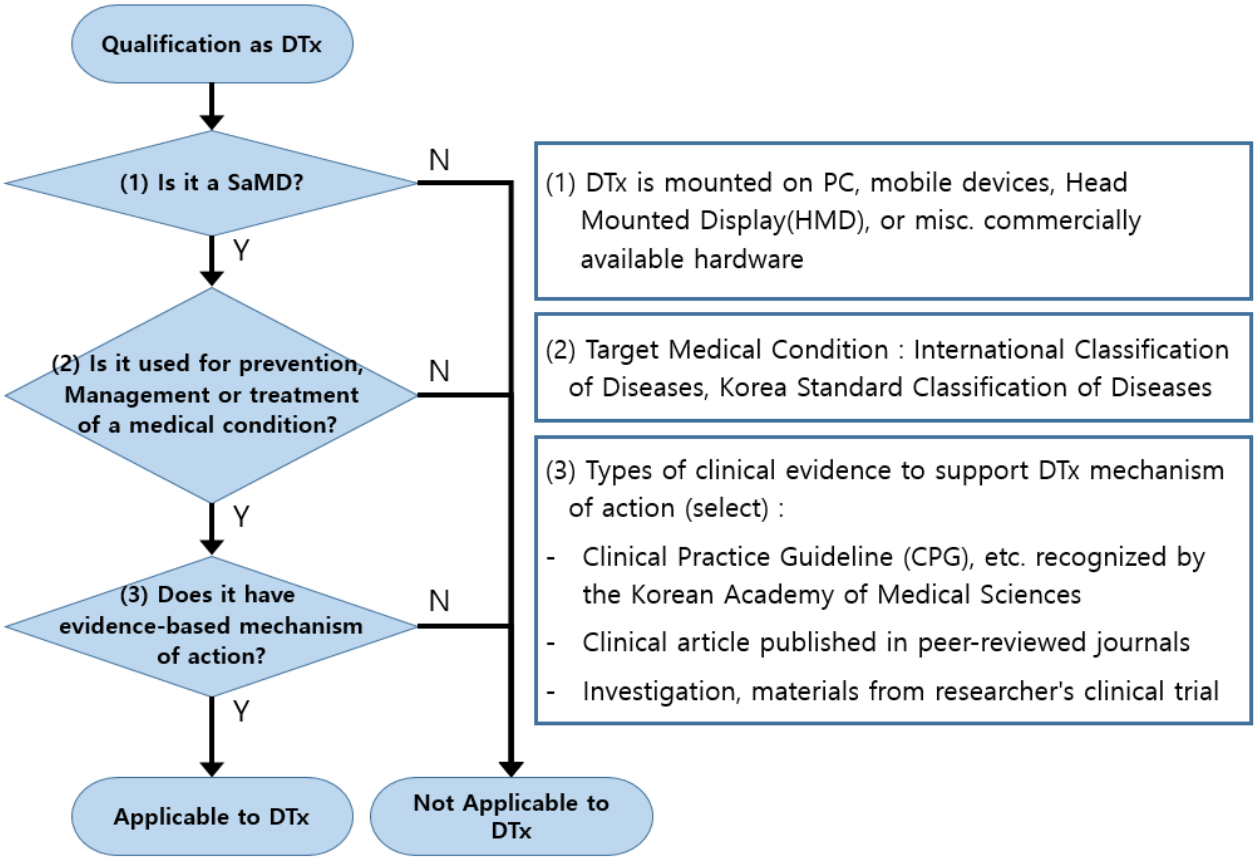
A prospective study, sometimes called a prospective cohort study, is a type of longitudinal study where researchers will follow and observer a group of subjects over a period of time to gather information and record the development of outcomes.

II Criteria and Examples of Digital Therapeutics

Whether a device falls under the category of a DTx will be comprehensively determined by the intended use stated in Article 2 of the Medical Devices Act and the criteria as shown in the diagram below.

However, depending on the criteria, a device that does not fall under the a DTx requirements may or may not be categorized as a medical device.

In order to determine whether the product is a medical device, its intended use should meet the definition of the Article 2 of the Medical Devices Act, and should be evaluated according to the manufacturer's intention: structure/shape of the product, intended use and effect, and advertisement/explanation for the sales.



< Figure. Decision Making Flowchart>

Examples of products that may qualify as a DTx are given below:

Even if the product corresponds to any of the examples below, clear documentation that proves scientific or clinical evidence of its mechanism of action is required to qualify as a DTx. Also, depending on its features (applicable patients, mechanism of action, etc.), the product may be classified as a DTx in a variety of clinical fields.

<Examples>

[Prevention and Management]

o Software for preventing the recurrence of epilepsy through cognitive behavior correction and relaxation therapy for patients with epilepsy

o Software for preventing blurred vision by controlling the dosage of medication according to the visual acuity test values of patients with macular and posterior pole degeneration

o Software for preventing Alzheimer's disease through cognitive rehabilitation training for patients with mild cognitive impairment

o Software for reducing the frequency of schizophrenic symptoms through treatment and control of the dosage of medication for patients with schizophrenia

o Software for managing the side effects of drugs by controlling the dosage of medication and monitoring nausea and pain of patients with stomach cancer

o Software for managing the recurrence of migraines through cognitive behavioral therapy for patients experiencing migraines

o Software for managing sarcopenia through interventions of exercise intensity and rehabilitation training for patients with sarcopenia

o Software for maintaining normal blood pressure by monitoring blood pressure and controlling antihypertensive drugs for patients with hypertension

o Software for maintaining and managing normal blood glucose levels by controlling the dosage of medication according to the blood glucose level of patients with insulin dependent diabetes

[Treatment]

o Software for enhancing physical abilities and reducing dyspnea symptoms through load adjustable therapy within the scope of high intensity for respiratory rehabilitation of patients with chronic obstructive pulmonary disease (COPD)

o Software for managing smoking withdrawal through cognitive behavioral therapy for patients with mental and behavioral disorders caused by smoking

o Software for reducing symptoms of bipolar disorder through cognitive behavioral therapy for patients with bipolar disorders

o Software for reducing tremors through control of the dosage of medication (levodopa) by analyzing the conditions of patients with Parkinson's disease

o Software for reducing the frequency of symptoms (dyspnea, cough, etc.) through virtual reality programs for patients with asthma or COPD

o Software for treating alcoholism through cognitive behavioral therapy for patients with mental and behavioral disorders caused by alcoholism

o Software for treating chronic insomnia through cognitive behavioral therapy for patients with chronic insomnia

o Software for treating major depressive disorder through psychological education and cognitive behavior correction for patients with the depressive disorders

o Software for treating schizophrenia through cognitive behavioral therapy for patients with schizophrenia

o Software for treating avoidance through exposure therapy applying virtual reality to patients with post-traumatic stress disorder

o Software for treating binge eating behaviors through cognitive behavioral therapy for patients with bulimia nervosa

o Software for treating functional defecation disorders through cognitive behavioral therapy for patients with irritable bowel syndrome

III Review and Approval Method

1. Preparation for Technical Documents

In accordance with Articles 8 to 18 of the Regulation, technical documents of medical devices must include the following information:

1. Name (product name, title of product group, model name)
2. Classification number (class)
3. Shape & structure – mechanism of action, external figure, dimensions, features
4. Raw materials
5. Manufacturing method
6. Performance
7. Intended use
8. Usage
9. Precautions
10. Packaging unit
11. Storage method and shelf-life
12. Test specifications
13. Manufacturer (for importation or contracting out in whole manufacturing process)

14. Approval conditions
15. Remarks

A DTx is included in the SaMD category. Therefore, we recommend that you refer to the section "V. How to prepare technical documents for medical device software" of the "Guidance for the Review and Approval of Medical Device Softwares" if you prepare technical documents for a DTx. With the above elements, the following information must be considered and described because of the characteristics of a DTx.

A. Shape and Structure –Mechanism Of Action

For mechanism of action, the scientific or clinical principles that were applied to achieve the intended use (efficacy and effectiveness) of a DTx shall be described in accordance with the "mechanism of action" as stated in Article 9 (Shape and Structure) of the Regulation. The supporting documents shall meet one of the standards provided in section "II. Judgement Criteria for Digital Therapeutics - (3) Types of scientific evidence of the mechanism of action" of this guidance. It should be noted that any clinical efficacy and/or effectiveness that has not been explained in the supporting documents should not be mentioned.

< Types of scientific (clinical) evidence of the mechanism of action >

- Clinical Practice Guideline (CPG), etc. recognized by the Korean Academy of Medical Sciences
- Clinical article published in peer-reviewed journals
- Documents on investigational or researcher's clinical trial

B. Intended Use

For intended use, the information pertaining to the targeted patients and diseases that need treatment, prevention, and management should be described in accordance with the Article 12 (Intended use) of the Regulation.

C. Performance

For performance, the information pertaining to the hardware requirements, encryption methods (standard), and a software operation (driving) system, such as the OS, CPU, RAM, HDD, and communication methods should be described in accordance with Article 12-2 (Performance) of the Regulation.

For major features, items should be described that can confirm the effectiveness of the product, such as management, prevention, and treatment applied to treat medical disorders or diseases.

D. Precautions

For precautions, all safety information should be described to ensure safe and reasonable use of the product in accordance with Article 14 (Precautions for use) of the Regulation.
Other factors that must be mentioned include the use of the product by a doctor's prescription, precautions for when using the product alone, and information of which the safety and effectiveness have not been evaluated.

E. Test Specifications

For test specifications, the test items, test criteria, and test methods for the performance and

encryption method or standard of the product should be described in accordance with Article 17 (Test Specification) of the Regulation. The test items for product performance shall be selected based on the main functions of the product, while the test criteria and test method shall be stated considering the features of the product.

2. Submissions for Review and Approval

Submissions for obtaining review and approval of medical devices shall comply with Article 26 (Types and Scope, Etc of Information to be reviewed) and Article 29 (Requirements of Submissions) of the Regulation. The submissions are as follows.

1. Substantial equivalence report
2. Documents on the intended use
3. Documents on the mechanism of action
4. Documents on electrical/mechanical safety
5. Documents on biological safety
6. Documents on safety related to radiation
7. Documents on safety related to electromagnetic waves
8. Documents on performance
9. Documents on physical/chemical features
10. Documents on stability
11. Documents on the origin or discovery, and development of the product
12. Documents on clinical trials
13. Documents on product use in other countries

A DTx requires the submissions including a substantial equivalence report which compares the pre-approved medical device and the new medical device, documents on the intended use, documents on the mechanism of action, documents on the performance, documents on the

origin/discovery/development, documents on the clinical trials, and documents on the usage of the product in other countries when applying for review and approval as SaMD. With the above elements, the following information must be considered and described because of the characteristics of a DTx.

A. Documents on the Mechanism Of Action

Documents on the mechanism of action shall explain how scientific (clinical) evidence is applied in realizing the intended use of the product for patients. Also, these documents shall comply with one of the items listed on "II. Criteria of Digital Therapeutics - (3) Types of scientific or clinical evidence of its mechanism of action."

< Types of scientific or clinical evidence of the mechanism of action >
- Clinical Practice Guideline (CPG), etc. recognized by the Korean Academy of Medical Sciences
- Clinical articles published in peer-reviewed journals
- Documents on investigational or researcher's clinical trial

B. Documents on Performance

A DTx as a software requires the submission of Attached Form 13 in accordance with Attached Table 13: "Software Conformity Assessment Report" and "Documents on Software Verification and Validation". If a product features wire and wireless communication, additional information including cybersecurity on how to block forgery and unauthorized access must be included in the section on "Documents on Software Verification and Validation".

As for cybersecurity, please refer to the “Guidance for the Review and Approval of Cybersecurity for Medical Devices” and submit a document containing the “Table 3. Requirements for Cybersecurity of Medical Devices” of the guidance.

C. Documents on Clinical Trials

Documents on clinical trials demonstrating the safety and effectiveness of a DTx should comply with the Article 29 (Requirements of Attached Information) and sub-paragraph 12 (Documents on Clinical trials) of the Regulation. Therefore, the supporting documents that show the safety and effectiveness of the product ensured by conducting prospective clinical study should be submitted.

However, pilot study may be necessary prior to confirmatory clinical trials if the product is in the development stage, depending on the existence of scientific or clinical evidence on its therapeutic mechanism.

If the pilot study are for creating evidence for the therapeutic mechanism, the applicant can extract some part of the article or literature on similar products and submit them instead of the “scientific or clinical evidence of its mechanism of action”, which was previously mentioned.

As a result, before conducting confirmative clinical trials for a DTx, these documents - clinical articles, clinical treatment guidelines, or exploratory clinical trials for scientific (clinical) evidence on the mechanism of action should be prepared.

Also, applicant should keep updating the RWE data utilized and collected the real RWD in practical clinical environment in order to monitor the potential benefit and risk of the product since its approval, and MFDS may require to applicant to submit this data, if necessary.

For more information on preparing submissions of RWE, please see the “Guidance for Real World Evidence (RWE) Application in Medical Devices”.

< Items to be Included in the Documents on Clinical Trials >

1) Method of clinical trials

The method of clinical trials shall include the following:

a) Selection and exclusion criteria, and target number of subjects

Documents proving the sample size of clinical trial was properly determined in a statistical way by considering the characteristics and clinical trial methods of the product for each indication should be submitted in principle. However, applicants may be required to submit the additional supporting documents in case they are not able ensure the sample size due to the lack of sufficient case studies of indications of the diseases.

b) How to operate or use the product and the grounds (reasons) for method of clinical trials

c) Grounds in case the comparable device is used

d) Concomitant administration

e) Items of observations, measurements, clinical laboratory test, measurement criteria, and test methods

f) Evaluation criteria, evaluation methods, interpretation methods for effectiveness

g) Evaluation criteria and testing methods for safety including side effects

2) Results of clinical trials

The results of clinical trials shall include the following:

a) Clinical trial results (They shall include the planned number of clinical cases, actual number of subjects, number of subjects that completed the trial, number of dropouts and

the reason. In this case, the side effects of each subject shall be included.)

b) Summary of case records

c) Other documents required for clinical trial results

3) Clinical evaluation

Documents that prove the clinical significance of the effectiveness of medical devices based on the medical/Korean medical principles. This can be recognized if the effectiveness is acknowledged.

※ Should it be considered that the application of foreign clinical trials~~s~~ data is difficult due to differences in ethnic factors, the Minister of Food and Drug Safety may request additional data with Korean subjects.

3. Subjects to Change Approval and Review

If a DTx has any changes in accordance with Article 6 of the Medical Devices Act, the approval for the product may be subject to be re-evaluated according to Article 12 of the Act. When applying for approval for changes, the product may be subject to a "review of clinical documents" or "review of technical documents" if the product has any significant change that may affect to the safety and effectiveness such as characteristics, main functions, intended use.

A. Subject to Review of Clinical Documents

1) For changes in the intended use of pre-approved products (addition or change of indications)

※ e.g. Addition of indication: (Before change) Dementia → (After change) Dementia and cognitive impairment

※ e.g. Change in indication: (Before change) Dementia → (After change) Epilepsy

2) For changes in the mechanism of action (addition or change)

3) For any case that affect the safety and effectiveness

B. Subject to Review of Technical Documents

1) For changes in programming languages and operating system, etc of medical device software

※ e.g. Android → iOS

2) For changes, addition, deletion of the software do not affect the intended use and mechanism of action of the product

IV References

1. Guidance on the Review and Approval of Cyber Security for Medical Devices (MFDS, November 2019)
2. Guidance on the Review and Approval of Artificial Intelligence (AI)-based Medical Devices (MFDS, October 2019)
3. Guidance on Clinical Trials Design of Artificial Intelligence(AI)-based Medical Devices (MFDS, October 2019)
4. Guidance on the Review and Approval of Medical Device Software (MFDS, September 2019)
5. Guidance on the Application of Real World Evidence in Medical Devices (MFDS, February 2019)
6. Guidance on the Review and Approval of the Medical Devices Applied with Virtual and Augmented Reality technology (MFDS, June 2018)
7. Digital Therapeutics Alliance (DTA) website: https://www.dtxalliance.org/

Digital Health Devices Division

Medical Device Evaluation Department

National Institute of Food and Drug Safety Evaluation

Ministry of Food and Drug Safety

Email: digitalhealth@korea.kr

https://www.mfds.go.kr/eng/medicaldevice.

MINISTRY OF FOOD AND DRUG SAFETY

National Institute
of Food and Drug Safety Evalution

Medical Device Evaluation Department