The content on this webpage was developed by NIH SEED based on its collective experience working with the NIH innovator community. This information has been developed, for informational purposes, to address questions frequently asked by NIH awardees, and represents the experiences of the subject matter experts who contributed to its development.

Regulatory Knowledge Guide for Digital Health

NIH SEED Innovator Support Team

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Introduction

The broad scope of digital health includes categories such as mobile health, health information technology, wearable devices, telemedicine, and personalized medicine. In each of these cases, digital health technologies empower consumers (patients, healthy individuals, and anywhere in between) to make better-informed decisions about their health.

The U.S. Food and Drug Administration's (FDA) **Center for Devices and Radiological Health** (CDRH) fosters innovation of digital health products through the Digital Health Program. CDRH has been regulating software for many years as components of therapeutic devices or as medical devices in their own right (so-called **Software as a Medical Device** (SaMD)). However, the digital health space of **artificial intelligence/ machine learning** (AI/ML), cloud-based computing and data-sharing, wearables, and mobile apps is relatively new and rapidly developing. When these technologies are determined to be regulated digital health products, CDRH is the regulatory authority and oversees the Market Authorization process for them.

Identifying Which Digital Health Products Are Regulated

Determining if the technology is a regulated digital health product early in the process is key. Why? Because a digital health product *may or may not* be regulated by FDA.

How do you make this determination? By examining the intended use of the new technology—which is how CDRH categorizes digital health products. First, you must determine if your technology is a medical device. If it is, you need to decide whether CDRH is likely to practice "enforcement

discretion"—meaning FDA does not intend to enforce regulatory requirements for specific types of devices.

If the digital health technology is a medical device and it does not fall under FDA's "enforcement discretion," you will need follow one of the Market Authorization processes outlined below.

If the intended use is for the diagnosis, cure, mitigation, treatment, or prevention of disease (or to affect the structure/function of the body), the product is a medical device. Digital health technologies that are classified as medical devices are subject to the same pre-market and post-market requirements as therapeutic devices or *in vitro* diagnostics.

Digital Health Products

• Software apps that are not medical devices	Not regulated
• Software devices under enforcement discretion	Not regulated
• Software as a Medical Device (SaMD)	Regulated

It is critical to understand where your technology falls within these categories. Because the categorization is based on the intended use (not the underlying algorithms or platforms), it is possible that different versions of a given product may fall into different categories.

In this guide, CDRH requirements for regulated digital health products are described along with other relevant tips to help guide you through the regulatory process.

NIH SEED: SaMD and AI/ML Regulatory Workshop
NIH SEED: NIH Digital Health Info Session
NIH SEED: Digital Health Town Hall
NIH SEED: FDA CDRH Registration and Listing Requirements

Technologies Not Covered in This Guide

Deciding which version of technology to bring to market is a business decision that may have significant regulatory impact. If the software technology is not an app or a technology that is under FDA enforcement discretion (see FDA guidance on enforcement discretion), contact the Division of Digital Health to determine if regulations apply.

Examples of Technologies and Software Apps That Are Not Regulated

- Educational/training software
- Hospital administration automation
- Mobile apps platforms
- HIPAA compliant app for communication with healthcare providers

- **Digital health development activities that are linked to basic clinical research and are not directly leading to commercialization**

For medical devices that fall under FDA's enforcement discretion and are considered low risk, no additional regulation is required. FDA specifies that devices under enforcement discretion include those that help patients self-manage their disease or condition without providing specific treatment suggestions; or those that automate simple tasks for healthcare providers.

Examples of Devices That Are Not Regulated Because They Fall Under Enforcement Discretion

- **Software to aid patients with psychiatric conditions**
- **Games to encourage physical therapy at home**
- **Apps that use patient characteristics to recommend counseling or preventative services**
- **Software that aggregates and displays trends in personal health incidents**

In addition, there is a NIH Small Business Education and Entrepreneurial Development (SEED) Digital Health webinar, Digital Health Info Session, and regulatory case study (listed below) that provides more in-depth discussion and examples on managing the multiple tasks related to moving new innovations through the regulatory process.

Link to Medical Device Regulatory Case Study #1

If you are unsure whether your digital health technology is regulated by FDA, the NIH Office of Extramural Research (OER) Small Business Education and Entrepreneurial Development (SEED) team recommends you contact digitalhealth@fda.hhs.gov.

Please use the Word navigation panel to jump to sections that are relevant for your specific needs. Bolded terms within the text are defined in the Glossary.

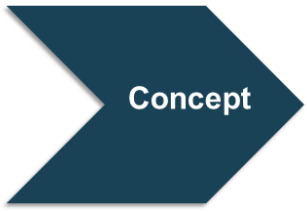
If you have additional questions or want to connect with someone to discuss your specific situation, contact the SEED Innovator Support Team.

Key Takeaways

After reading this Regulatory Knowledge Guide, you will have a better understanding of these important aspects of digital health product development.

- When a digital health product is regulated by FDA, it is considered a medical device and is subject to applicable regulatory processes.
- Documentation of software systems and subsystems is a fundamental part of FDA review; these documents are used to assess your software quality.
- Digital health, mobile medical apps, artificial intelligence, and machine learning are rapidly changing technologies—ensure you are leveraging the most recent news, guidance, and policies from FDA.
- If an algorithm is informed by curated training data (e.g., AI/ML), it should be validated on data that accounts for the intended use population.

Table of Contents



1 Software Design and Feasibility

If your technology is very early in its development, a variety of active research may be ongoing simply to prove whether the idea is feasible. Such research does not generally fall under FDA oversight. However, after you have successfully demonstrated the feasibility of your approach, you will need to create a new plan to confirm/validate the performance of the device. It is helpful to think of confirmatory testing (Section 2) as a separate step entirely from the proof-of-concept feasibility research.

In the case of digital health products, it is particularly important to include elements of a software quality system as early in the development as possible—ideally during feasibility testing. FDA provides specific guidance on the documentation for software contained in medical devices.

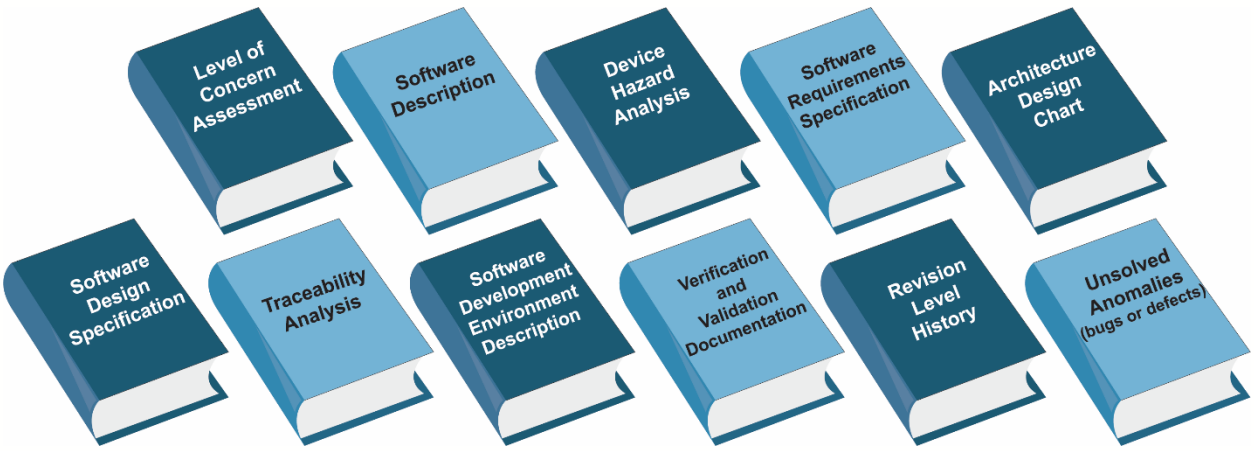


Figure 1. Types of Documentation for Software Contained in Medical Devices

1.1 Design Requirements

Tracking the requirements of each of the software modules is integral to a functional software quality system and is an expectation from CDRH to ensure safe and effective medical devices. Even at an early stage of development, it is highly beneficial to verify and update each of the software modules.

Digital health products consist of several software modules and typically include:

- User interface
- Data handling system
- Algorithm to process inputs into interpretable outputs

As you test the feasibility of your product, track the individual requirements and performance of these functional units. These may include hardware requirements, interface requirements, or internal software tests, checks, and error-handling. These requirements will eventually be documented and submitted to FDA as part of your Software Requirements Specifications. (see page 13 of the pre-market medical device software guidance.)

Traceability—links between designs, requirements, and tests—is a key element of a software quality system, and a focal point of FDA review.

There can be many, many software modules within a given digital health product, and they can be handled by a wide range of software development practices. CDRH requires verification of the functionality of the device but does not dictate how to verify it (that is up to the innovator). The earlier you establish a defined set of software practices, the better for the quality of your product.

Whether the end user of the digital health product is a doctor, a patient at a clinic, or a family at home, it is important to design the device to meet user needs. When CDRH reviews software design as part of a Market Authorization application, they check to ensure that the software development is clear, is unambiguous, and has minimal ad hoc design decisions. There should be a reason for each design choice, and user needs should be met by the product as a whole.

It is up to you to determine the goals of your product, based on technical and clinical constraints. Be deliberate in recording and updating your design process as you continue to optimize your software. One tactic to ensure you are developing a device that will meet user needs is to formally survey your intended users. For example, if you are developing a radiological software tool, you could find actual radiologists to learn about their workflow and needs. Users are often eager to help improve a product design, and you should have a process to incorporate their feedback.

1.2 Verification and Validation

One of the most important regulatory aspects of digital health technologies is **verification** and **validation** (V&V). Through V&V, you prove that the device functions as necessary to perform its intended use—whether that involves specific levels of accuracy or precision, pass/fail testing of software modules, and/or clinical confirmation. A finished product may have a long list of different V&V activities. The V&V plan will be a primary focus for FDA reviewers to ensure that the safety and effectiveness of the technology has been rigorously demonstrated.

Because the V&V plan is important not only for regulatory considerations but for product development and commercialization, you should develop a software test plan as soon as possible.

Your performance testing (bench, clinical, and computational) should link to the V&V specific functional/design requirements. In your eventual Market Authorization application, these links are formally documented in the **traceability analysis** (see page 13 of the pre-market software guidance). If the V&V relies on human testing, refer to the guidelines in Section 2.

1.3 Data Considerations

For digital health technologies, the source of data is important for early and late phases of development. This is especially true in the development of **artificial intelligence/machine learning** (AI/ML) algorithms which are primarily derived from large sets of data. Ensure you have access to both the *type* of data (e.g., historical, clinical, real-world, or simulated), and know the *amount* of data your feasibility testing will require.

See also Section 2.2 to ensure the testing dataset is representative (or generalizable) to the intended use population.

Your data should include separate **training data** and **testing data**. Training data is the data used to develop the technology and is typically not part of regulatory oversight. Testing data is the data used to prove the technology is safe/effective and is very important to FDA. These two distinct datasets need to be isolated from one another. Testing software on the training dataset is like testing a student who has already seen the exam. It will lead to over-confidence in the performance of the technology that will not extend to its use on the market.

If you are unable to find adequate data, you may need to reach out to academic or clinical collaborators to find the quality and quantity of the data required to develop your technology.

2 Confirmatory Testing

Confirmatory testing—validation that the device functions as intended—is a critical part of any regulatory plan. Sometimes referred to as pivotal studies, confirmatory testing is done after feasibility has been established. This verification of the device's performance may be a precursor to a statistically powered **clinical trial** for higher-risk devices. Or it may be sufficient testing on its own to demonstrate substantial equivalence. Whether testing occurs in humans, animals, computers, or test objects, you need to lay out a plan with pre-established criteria for success and carry it out.

You can refer to **510(k) summaries**, Premarket Approval (PMA) summaries of safety and effectiveness, or De Novo decision summaries for similar devices to better understand the testing requirements.

Note that all testing used to support a marketing application must be performed on the final finished form of the device.

2.1 Human Testing

The amount of data needed to support a device application varies. Some devices may require a large statistically powered clinical trial, which should be planned after confirmatory testing but may not be conducted until a later phase of development. Lower-risk devices may require human confirmatory testing only on a small number of healthy volunteers to demonstrate certain capabilities and

performance. Many software devices do not require human testing at all. In these cases, you can determine whether bench and animal testing, or modeling and simulation are sufficient to conform to general or special controls by looking up the regulation that corresponds to your device.

As with all human testing, your first step should be to consult with your Institutional Review Board (IRB).

The first line of protection for human subjects comes from the IRB overseeing the research. The IRB oversees the health and well-being of human subjects, and the ethics of the research involved. If any human testing will be done, the IRB needs to review and approve the study protocol. After review, the IRB may determine that the study needs to be referred to CDRH for additional oversight (such as an **Investigational Device Exemption** (IDE)).

While IDEs are generally used for large clinical trials, some devices may require an IDE for confirmatory testing as well. An IDE allows you to distribute some devices for investigational use in clinical practice before the device is approved. Often the IRB will advise whether an IDE is required based on experience with the device type and risk level.

However, not all human testing requires an IDE. Whether it does or does not depends on the risks involved with the testing plan. The IRB determines whether a risk-determination is needed from CDRH. Based on the technology and the intended use of the technology, along with the details of the proposed investigation, CDRH determines if the study poses **significant risk** (SR) or **non-significant risk** (NSR). If an IRB has determined a study is NSR, you do not need to confirm this with FDA to proceed with your research plan.

If the IRB suggests a **clinical trial** is SR and this is confirmed by FDA, an IDE will be required before human testing can begin. To request an IDE, you will need to present your study plans (size, methods, and success criteria) to CDRH, along with your risk mitigation strategy. If this is your first IDE application, FDA recommends that you request **a pre-IDE meeting** with CDRH.

NIH has a list of policies and information regarding IRBs and multi-site human testing. Furthermore, the Regulatory Guidance for Academic Research of Drugs and Devices (ReGARDD) group, funded in part by NIH's Clinical and Translational Science Awards, has produced an info page and short video on study risk determination. If you are uncertain about your device's risk level, you can review the FDA resources below to determine whether your product falls into those categories.

Devices that would require an IDE but are for humanitarian use—meaning they are intended to benefit patients (treatment/diagnosis) with diseases or conditions that affect not more than 8,000 individuals in the U.S.—are able to submit a Humanitarian Device Exemption (HDE) Program application. If you are proposing to investigate and/or market a device via an HDE application, your first step is to request a Humanitarian Use Designation from CDRH.

Resources:
FDA: IDE Application
FDA: Case Study: When Is an IDE the Right Choice?
NIH SEED: Investigational Device Exemptions (IDE) Applications and Pre-Submissions
FDA: IRB Responsibilities
FDA: Pediatric HDE Case Study
FDA: Significant Risk Vs. Nonsignificant Risk Studies Medical Device Studies
NIH: Multi-Site Human Testing IRB Policies
Article: ReGARDD Risk Determination and Video
Webinar: Humanitarian Device Exemption Program
NIH SEED: Humanitarian Use Devices

2.2 Data Requirements

While it is not required that training/developmental data represent the entire population, the final testing/confirmatory data will need to represent the entire intended population that will use that device. For example, if the device is intended for all adults, but was tested on student volunteers, then questions about its general performance could be raised. This is especially important in the development of AI/ML algorithms, which are primarily derived from large sets of data.

Be prepared to discuss the generalizability of the testing/confirmatory dataset, as well as its independence from the training data.

Final validation data should represent the intended use population—this is an important consideration for all medical devices, not just digital health technologies. But because digital health often relies on electronic patient data, be prepared to discuss the qualitative merits of your dataset with CDRH. What sub-populations are included or excluded? Do the results generalize? How are the dataset details communicated to the consumer/customer?

2.3 Cybersecurity Risk Mitigation Plans

Cyber threats to the healthcare sector have increased in frequency and severity. The need for effective cybersecurity to ensure medical device functionality and safety has never been more important. Not only is cybersecurity important for the reliability and useability of the medical product but it is also critical for the protection and integrity of patient data.

Due to the potential harm of growing cybersecurity threats, FDA requires innovators to identify and anticipate cybersecurity risks prior to applying for Market Authorization and to create a corresponding mitigation plan.

All digital health technologies submitted to FDA for review must have a cybersecurity risk mitigation plan in place.

This cybersecurity mitigation plan should be developed and implemented before large-scale testing on real patient data starts. Since it is a critical part of the software system, the cybersecurity plan will also need to be documented and submitted with the Market Authorization application.

If your digital health technology uses commercial off-the-shelf (OTS) software, review CDRH's OTS guidance document. You are responsible for the safety and cybersecurity of your digital health technology even if one of the OTS components leads to a failure.

CDRH has also provides extensive post-market cybersecurity considerations. Many of these can be addressed to improve the device's cybersecurity during development and validation.

Resources:
FDA: Off-The-Shelf Software Use in Medical Devices
FDA: Post-Market Management of Cybersecurity in Medical Devices
FDA: Content of Premarket Submissions for Management of Cybersecurity in Medical Devices
MITRE: Playbook for Threat Modeling Medical Devices

2.4 Direct Comparisons to an Existing Device

Side-by-side comparison to an existing device is not always required but can be a straightforward approach when cost/accessibility of the technology enable it. This mainly pertains to Class II devices and the 510(k) pathway**.** Using this method to demonstrate substantial equivalence is often cheaper and more direct than creating a new body of evidence.

If a suitable predicate device is available to you (whether it is already accessible or is straightforward to acquire), the validation of your technology can include a direct comparison to the predicate. For example, if you are developing a wearable over-the-counter electrocardiograph, you can compare the measurements from your technology to the measurements from an existing wearable monitor. The head-to-head comparison may not be sufficient validation on its own but it can provide a strong argument for substantial equivalence.

Furthermore, if the head-to-head comparison uses a current or prior version of your own technology as a predicate, the Special 510(k) program may be an option (providing a more streamlined review process). If this would be your first Special 510(k), contact CDRH to clarify that the path is open: this often involves a determination if the test methods are "well established."

On the other hand, if the existing technology is too expensive or otherwise burdensome to acquire, a side-by-side comparison is not required. Instead, a written discussion of similarities and differences can be included in your Market Authorization application, and an independent clinical or non-clinical validation can be performed.

2.5 Test Labs and Standards

There are internationally recognized **standards** for many components of a given device. For example, one ultrasound system may elect to conform to biocompatibility, sterility, electromagnetic safety and compatibility, usability, and software standards. There are also international standards for software development that can help establish and document the quality of the software.

Identify relevant standards by researching those used for similar products. If your technology does not meet the standards, you need to provide a justification to FDA why that does not raise new regulatory questions.

Some devices may not have any applicable standards, while others may have dozens. CDRH has a searchable database of recognized standards. Standards that are recognized by FDA provide sufficient test methods to demonstrate safety and efficacy of the technology within the context of that standard. For example, if your network connectable components conform to an FDA recognized cybersecurity standard, the testing described within the standard should be sufficient to validate your technology's safe networking capability.

Standards are not free, so consider whether to purchase the standards and perform the tests in-house. Note that some standards include tests that are readily and most cost-effectively performed by certified test labs. For example, if you cannot demonstrate the electromagnetic compatibility of a wearable device in your own lab (most cannot), you may want to send your device to a test lab.

You will need to document conformance to standards and include any test lab reports in your Market Authorization application.

Resource:
FDA: Recognized Consensus Standards

2.6 Artificial Intelligence and Machine Learning Algorithms

The AI/ML algorithms that support digital health technologies may have many variations, options, and parameters. If the underlying algorithm is not yet locked and finalized, you will need to complete verification before starting human testing.

Artificial intelligence and machine learning technologies are rapidly developing, and so too are their regulatory pathways.

You should carefully organize, track, and document all the locking, unlocking, validating, and testing of your algorithm throughout the development process. You may have several versions or forks of your digital health product that are actively under development. These should be organized in a way that enables you to track exactly which version was used for exactly which tests.

Any changes should be tracked in a highly detailed version control document, which FDA refers to as the "Revision Level History."

It is important that the underlying algorithm does not change during or after the human testing phase. The supporting validation must reflect the version of the device that will be on the market. Once the algorithm is locked and the design is frozen, those human testing data and results will be applicable for inclusion in your Market Authorization application.

Resources:
NIH SEED: SaMD & AI/ML Regulatory Workshop
FDA: Artificial Intelligence and Machine Learning in Software as a Medical Device Action Plan

3 Meeting with CDRH

You can meet with CDRH at multiple points and multiple times in the pre-market application process. For a more complete discussion of:

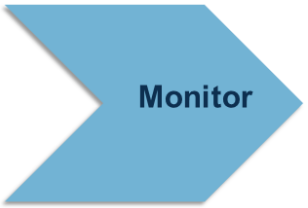
- Pre-submission meetings
- Pertinent **regulations**, product codes, and predicate devices
- **Intended use** and **indications for use** statements
- Test plans and preliminary results

please refer to the Regulatory Knowledge Guide for Therapeutic Devices.

4 Path to Market Authorization

There are different types of FDA Market Authorization applications for devices. Choosing which CDRH regulatory path to use—510(k), PMA, or De Novo—should be done early in the process.

For a more complete discussion of the different regulatory pathways, please refer to the Regulatory Knowledge Guide for Therapeutic Devices.



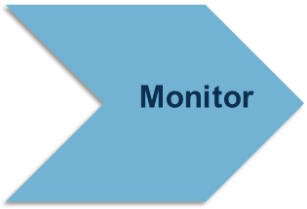
5 Manufacturing and Quality Management Systems

From a legal perspective, a software company that is marketing a digital health product is considered a manufacturer. Hence, the software company providing the digital technology in the Market Authorization application must adhere to manufacturing regulations of medical devices.

For a more complete discussion of manufacturing and **quality management systems** (QMS) of digital health technologies, including:

- Implementing QMS
- Complying with the Quality System Regulation
- International standards

please refer to the Regulatory Knowledge Guide for Therapeutic Devices and the NIH Quality Management Systems webinar.



6 Post-Market Changes to an Approved Technology

If changes are made to your device after it is granted Market Authorization in the U.S., you may need to submit a new Market Authorization application. For a more complete discussion about post-market changes to your device including:

- Evidence from outside the U.S.
- Major and minor changes to the device
- Changes to benefit risk ratio
- Conducting a new clinical trial
- **Real-world evidence** from clinical care

please refer to the Regulatory Knowledge Guide for Therapeutic Devices.

Changes to AI/ML are discussed below.

6.1 Updating AI/ML

AI/ML algorithms are the foundation of many new digital health products. These methods are data driven, meaning that their performance is only as good as the data used to develop them. Once your technology is on the market, the performance of the device may change over time as new data is gathered and processed. Carefully consider whether any changes significantly modify the functionality of the device.

Record all updates to the device in your internal QMS. Evaluate them to determine whether resubmission to CDRH is required. FDA has a guidance document to help you understand when a resubmission may be (or is) needed.

The data-driven nature of AI/ML makes the evaluation and re-evaluation of accuracy and performance even more important. AI/ML enables the software to improve based on experience.

However, unexpected trends in the data can produce unexpected results. CDRH policies for AI/ML are evolving. One of the approaches CDRH intends to utilize is a predetermined "Algorithm Change Protocol," which could be reviewed by FDA and allow for more streamlined AI/ML updates for devices on the market.

Resource:
FDA: Deciding When to Submit a 510(k) for a Change to an Existing Device