NIA SaMD & AI/ML Regulatory Workshop

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MITRE Medical Device [Digital] Regulatory Specialist

SEED (Small Business Education & Entrepreneurial Development)
NIA Healthy Aging Start-Up Bootcamp to Foster Diversity and Accelerate Innovation
23 August 2022

OFFICE OF EXTRAMURAL RESEARCH | OFFICE OF THE DIRECTOR | NATIONAL INSTITUTES OF HEALTH

NIH SEED

Agenda

Introduction

- **Overview of NIH SEED**
- **Two Speakers**

  Part 1 – Medical device pathways and software as a medical device expectations

  - **Break for questions**

  Part 2 – Recent landscape for AI/ML and enforcement discretion

  - **Break for questions**

Small Business Education and Entrepreneurial Development (SEED)

- Supports the NIH innovator community: validate scientific discoveries and advance them into healthcare products that improve patient care and enhance health.
- Collaborates with universities and research institutions, small businesses, trade associations and societies, angel investors, venture capitalists, and strategic partners.
- SEED leads initiatives that develop these relationships and build opportunities for NIH innovators to further their product development efforts.

Academic Innovation Team

National network of proof-of-concept centers that enables academic innovators access to product development expertise as they validate their technologies.

Includes 92 research institutions across 34 states and Puerto Rico.

SEED Small Business Team

SEED coordinates SBIR / STTR activities across the NIH Institutes and other HHS agencies.

NIH is the world's largest non-dilutive life sciences investor, backing over 1,000 companies annually with $1.2 billion in awards.

Innovator Support Team

Teams with experts in business and product development to offer education and mentorship. Support includes:

Product development guidance from industry veterans

Entrepreneurial training for NIH awardees and program staff

Strategic alliances with angels, VC, TTO's and state economic development agencies.

More at: seed.nih.gov

SEED Presenters from MITRE Health FFRDC*

Ben Berman, PhD
Medical Device Regulatory Specialist

Ben provides regulatory experience in medical devices to the SEED Innovator Support Team. Prior to supporting NIH, Ben worked at FDA in the Center for Devices and Radiological Health – both as a lead reviewer in the Division of Radiological Health, and as a research fellow in the Division of Imaging Diagnostics & Software Reliability. Ben is a contractor and part of the MITRE Labs Emerging Technology Innovation Center.

David Nahmias, PhD
Medical Device [Digital] Regulatory Specialist

David has extensive experience in development and regulatory aspects of digital health and AI/ML technologies. Prior to supporting NIH, David worked at FDA in the Center for Devices and Radiological Health as a researcher and review consultant in area of advanced patient monitoring as well as at the EHR Epic. David is a contractor and part of the MITRE Labs Health Innovation Center.

*** Federally Funded Research and Development Center**

Part 1 – Medical Device Regulation and SaMD

What is Digital Health?

- A Digital Health Product…
  - Utilizes computing platforms, connectivity, software, and/or sensors for healthcare
  - Includes categories such as
    - Mobile medical apps
    - Health IT
    - Wearables
    - Telehealth
    - Other software tools promoting personalized medicine
  - Spans range of use cases from general wellness to diagnostics
    - May or *may not* be a Medical Device

Source: FDA DHCoE

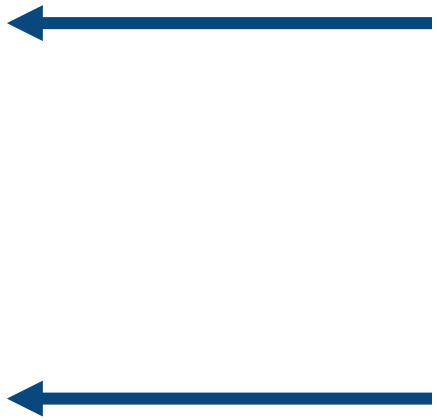
What is a Medical Device?

- A Medical Device is

  Any
  - Instrument
  - Machine
  - Contrivance
  - Implant
  - In-Vitro Reagent

  that is intended to
  - Treat
  - Cure
  - Prevent
  - Mitigate
  - Diagnose

  a disease.



the underlying technology (software/hardware)

+

what it is used for (Intended Use)

Source: FDA Device Advice

Software and Digital Health

- Many medical devices contain software
  - FDA guidance on how software design & validation should be documented
- In some cases, software is a medical device
  - Examples
    - Radiological image processing software tools
    - Smartphone apps that utilize external sensors

    → Regulated medical device

    - Video games to motivate physical therapy at home
    - Medication tracking tools

    → Medical device under *enforcement discretion*

    - Access to patient health records
    - Electronic medical dictionaries

    → Not a medical device
  - FDA guidance with more examples
- Software & Digital Health is a rapidly changing regulatory space
  - Federal Trade Commission – Interactive Tool

"Can you help me determine whether the FDA would consider my digital health product to be an actively regulated product?"

Yes – per FDA website, email DigitalHealth@fda.hhs.gov

Expectations of a SaMD

There are three main regulatory pathways to get your device on the market:

Premarket Approval (PMA)	De Novo Classification	510(k) Premarket Notification
Novel Devices and/or High Risk	Novel Devices with Controllable Risk	Not-Novel Devices with Controllable Risk

- SaMD devices that require a pre-market review are typically classified as Class II devices given their risk profile.
- Therefore, the 510(k) or De Novo pathway will likely be appropriate.

Pre-Submission Meetings with CDRH

- Pre-Submission Meetings (aka Q-Subs)
  - Serve a variety of purposes including
    - General questions ahead of an anticipated 510(k)/PMA/De Novo
    - Study risk determinations ahead of a potential IDE
    - Breakthrough device designation requests
    - Meetings held for an ongoing application
  - Free!
    - Formal detailed feedback from FDA experts within three months
    - Written, teleconference, or in-person
- One of these is a good Pre-Submission question:

How should we design our bench testing validation plan?

Does FDA agree that the bench testing plan, as we described, sufficiently quantifies the accuracy and precision?

Current Regulatory Landscape for AI/ML

- FDA obtained feedback on their proposed regulatory framework and most recently published an action plan
- Tools to assure safety and efficacy of AI-enabled devices are not as well understood as other technologies
- Introduction of concepts like an algorithm change protocol (ACP) are examples of adaption to changing landscape

https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device

Part 2 – Recent Landscape for AI/ML Enforcement Discretion

CDRH Digital Health Center of Excellence

Established in Fall 2020

A rapidly developing regulatory landscape

Our goal: Empower stakeholders to advance health care by fostering responsible and high-quality digital health innovation.

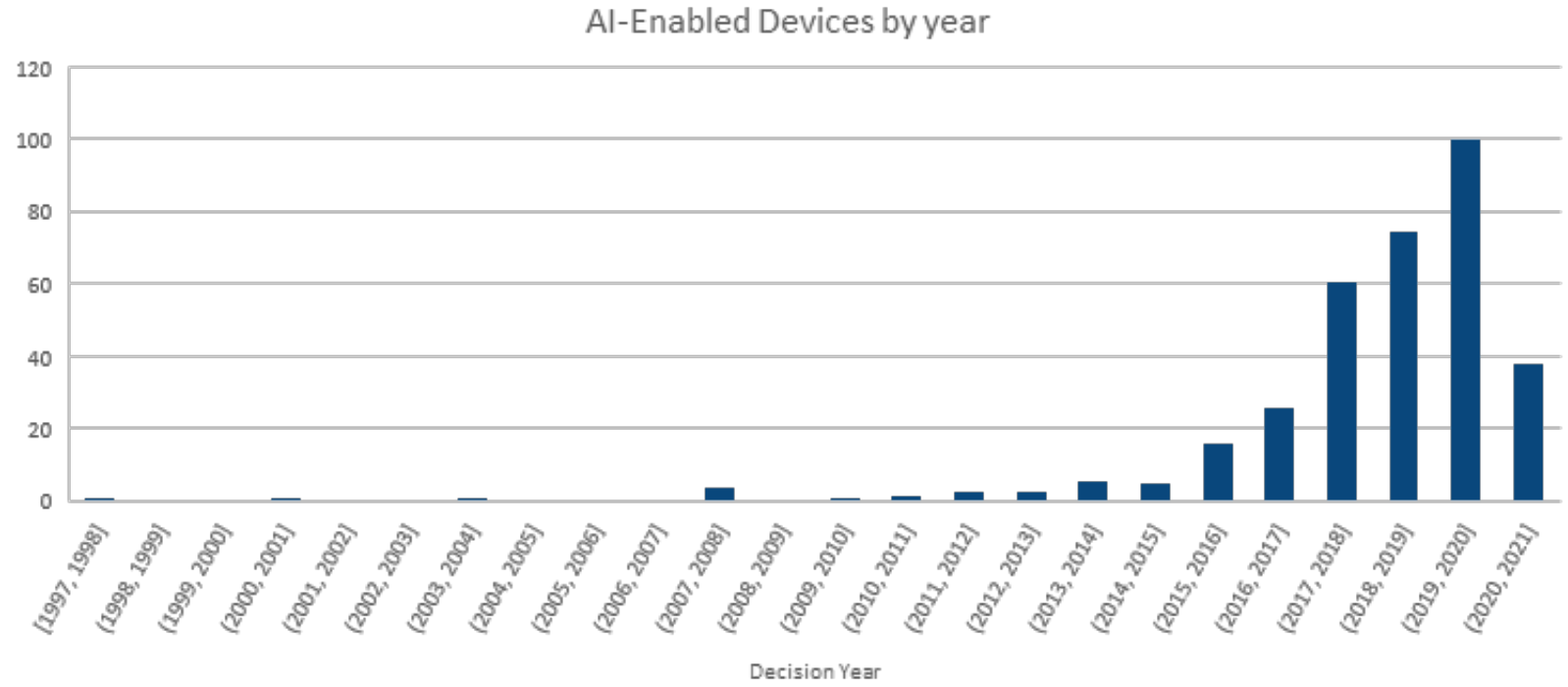
Our objectives: The Digital Health Center of Excellence aims to:

- **Connect and build partnerships** to accelerate digital health advancements.
- **Share knowledge** to increase awareness and understanding, drive synergy, and advance best practices.
- **Innovate regulatory approaches** to provide efficient and least burdensome oversight while meeting the FDA standards for safe and effective products.

Source: FDA DHCoE

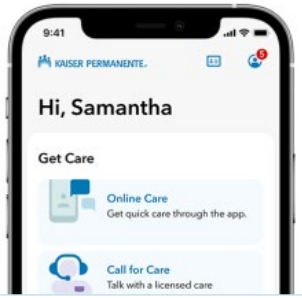
Current Regulatory Landscape for AI/ML

- Evolving field, AI/ML enabled devices have become more common in recent years and FDA has had to react to the fast changing and complex methods used within the devices.
- FDA (non-comprehensive) lists 343 cleared devices (all Class II) that utilized AI/ML, majority were reviewed by radiology panel (240/343).



When is a Digital Health Product regulated? – Part 1

1. If a Digital Health Product is not a medical device (by definition), then it is **not** regulated by FDA CDRH.
   - Examples
     - Access to patient health records
     - Electronic medical dictionaries
     - Educational or training tools
   - Federal Trade Commission Interactive Tool
     - HIPAA Rules (Office for Civil Rights), among others, may still apply



Contains Nonbinding Recommendations

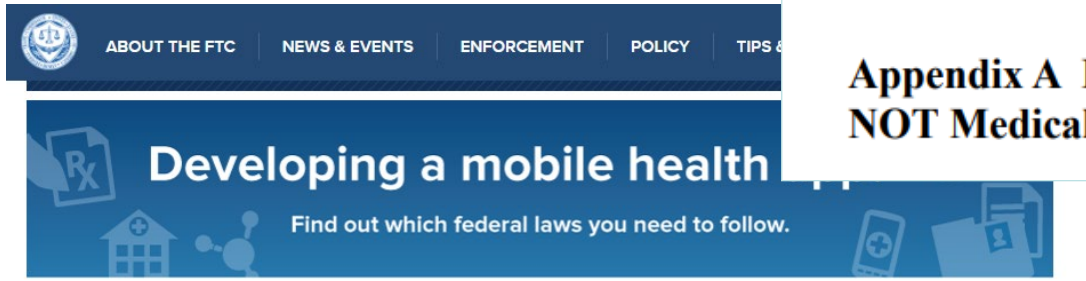
Policy for Device Software Functions and Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 27, 2019.

Appendix A Examples of Software Functions that are NOT Medical Devices

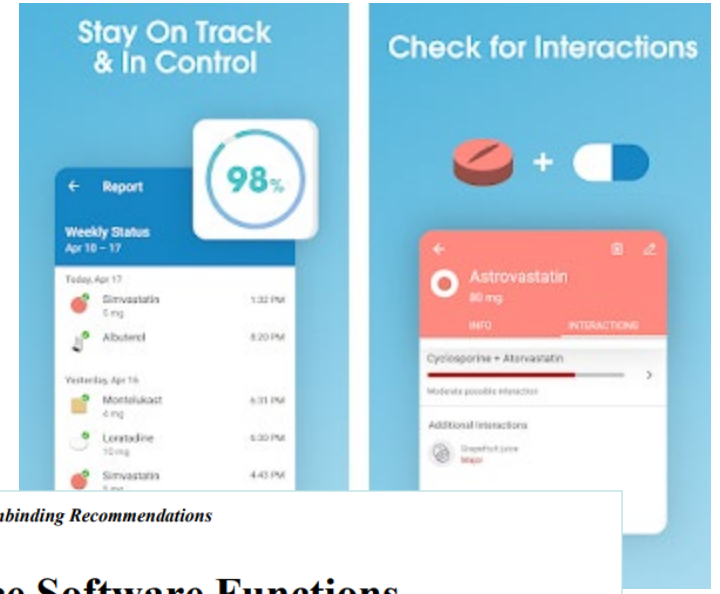
Source: CDRH Guidance



Source: FTC

When is a Digital Health Product regulated? – Part 2

2. If a Digital Health Product is a *low-risk* medical device, then it may be under **enforcement discretion.**
   - Examples
     - Video games to motivate physical therapy at home
     - Medication tracking tools
   - Innovators can reach out to FDA to confirm!
     - Start with an email
     - If more info is needed, a Q-submission can be scheduled



"Can you help me determine whether the FDA would consider my digital health product to be an actively regulated product?"

Yes – per FDA website, email DigitalHealth@fda.hhs.gov

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Appendix B Examples of Software Functions for which FDA intends to exercise enforcement discretion

Source: CDRH Guidance

When is a Digital Health Product regulated? – Part 3

3. *Otherwise*
   - It is a medical device
   - It has moderate, greater, or uncertain risks

the Digital Health Product is regulated.

- Examples
  - Radiological image processing software tools
  - Smartphone apps that utilize external sensors
- Same regulatory processes/requirements as any medical device.
  - **510(k)**: substantial equivalence
  - **De Novo**: new product; paving the way for future 510(k)
  - **PMA**: new/high-risk product; safety & efficacy via clinical studies
  - Post-market compliance: quality systems, adverse event reporting, …

Contains Nonbinding Recommendations

Policy for Device Software Functions and Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 27, 2019.

Appendix C Examples of Software Functions that are the focus of FDA's regulatory oversight (Device Software Functions and Mobile Medical Apps)

Source: CDRH Guidance

Risk – the Key Ingredient

- Risk informs all regulatory pathways
  - Enforcement discretion
  - 510(k)
  - De Novo
  - PMA
- The International Medical Device Regulatory Forum (IMDRF) has created guiding principles for software risk assessment.

State of Healthcare situation or condition	Significance of information provided by SaMD to healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV.*i*	III.*i*	II.*i*
Serious	III.*ii*	II.*ii*	I.*ii*
Non-serious	II.*iii*	I.*iii*	I.*i*

Figure - SaMD Categories

IMDRF principles are not U.S. regulatory requirements

A tool to help innovators set expectations and **begin** the dialog with FDA.

Source: IMDRF

Case Study: AI/ML-Enabled SaMD

Example of recent AI/ML device's indication for use description

Indications for Use *(Describe)*

Saige-Q is a software workflow tool designed to aid radiologists in prioritizing exams within the standard-of-care image worklist for compatible full-field digital mammography (FFDM) and digital breast tomosynthesis (DBT) screening mammograms. Saige-Q uses an artificial intelligence algorithm to generate a code for a given mammogram, indicative of the software's suspicion that the mammogram contains at least one suspicious finding. Saige-Q makes the assigned codes available to a PAS/EPR/RIS workstation for worklist prioritization or triage.

Saige-Q is intended for passive notification only and does not provide any diagnostic information beyond triage and prioritization. Thus, it is not intended to replace the review of images or be used on a stand-alone basis for clinical decision-making. The decision to use Saige-Q codes and how to use those codes is ultimately up to the interpretating radiologist. The interpretating radiologist is responsible for reviewing each exam on a diagnostic viewer and evaluating each patient according to the current standard of care.

Case Study: AI/ML-Enabled SaMD

Example of recent AI/ML device

Indications for Use

The ECG app is a software-only mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel electrocardiogram (ECG) similar to a Lead I ECG. The ECG app determines the presence of atrial fibrillation (Afib) or sinus rhythm on a classifiable waveform. The ECG app is not recommended for users with other known arrhythmias.

The ECG app is intended for over-the-counter (OTC) use. The ECG data displayed by the ECG app is intended for informational use only. The user is not intended to interpret or take clinical action based on the device output without consultation of a qualified healthcare professional. The ECG waveform is meant to supplement rhythm classification for the purposes of discriminating AFib from normal sinus rhythm and not intended to replace traditional methods of diagnosis or treatment.

The ECG app is not intended for use by people under 22 years old.

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Electrocardiograph software for over-the-counter use. An electrocardiograph software device for over-the-counter use creates, analyzes, and displays electrocardiograph data, and can provide information for identifying cardiac arrhythmias. This device is not intended to provide a diagnosis.

NEW REGULATION NUMBER: 21 CFR 870.2345

CLASSIFICATION: Class II

PRODUCT CODE: QDA

BACKGROUND

DEVICE NAME: ECG App

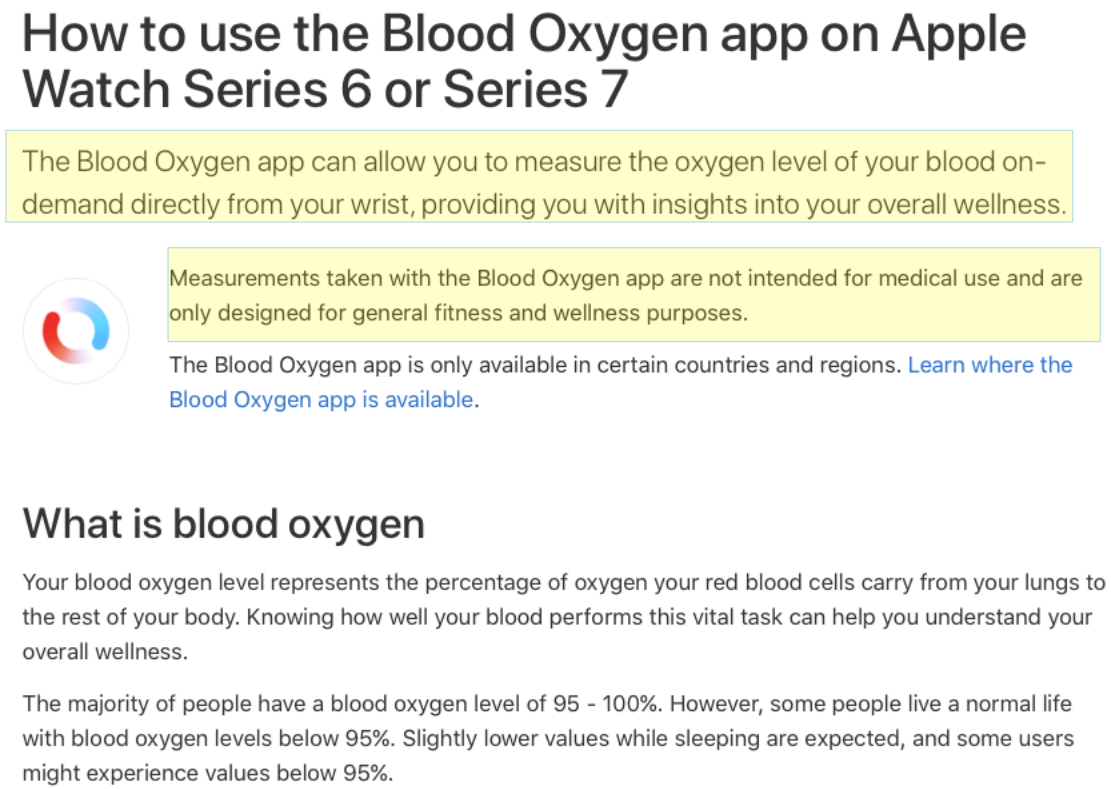
SUBMISSION NUMBER: DEN180044

DATE OF DE NOVO: August 14, 2018

CONTACT: Apple Inc.
One Apple Park Way
Cupertino, CA 95014

Case Study: AI/ML-Enabled Digital Health Product

Example of recent AI/ML digital health product (not FDA cleared)



How to use the Blood Oxygen app on Apple Watch Series 6 or Series 7

The Blood Oxygen app can allow you to measure the oxygen level of your blood on-demand directly from your wrist, providing you with insights into your overall wellness.

Measurements taken with the Blood Oxygen app are not intended for medical use and are only designed for general fitness and wellness purposes.

The Blood Oxygen app is only available in certain countries and regions. Learn where the Blood Oxygen app is available.

What is blood oxygen

Your blood oxygen level represents the percentage of oxygen your red blood cells carry from your lungs to the rest of your body. Knowing how well your blood performs this vital task can help you understand your overall wellness.

The majority of people have a blood oxygen level of 95 - 100%. However, some people live a normal life with blood oxygen levels below 95%. Slightly lower values while sleeping are expected, and some users might experience values below 95%.

Comparing the previous example and this example: Two digital health products, one with FDA approval and the other not requiring FDA approval (under enforcement discretion), can share the same hardware.

Case Study: AI/ML-Enabled Digital Health Product

Example of recent AI/ML digital health product (not FDA cleared)

About Headspace

Headspace was started with one mi
health and happiness of the world.

Two years ago, Headspace announced it would seek FDA approval, with the hope of becoming the first "prescription meditation" app. The company hoped to get approval for an undisclosed indication in 2020, but has not yet shared new details on its timing or the specifics of what it will pursue.

10. MEDICAL DISCLAIMER

10.1 Headspace is a provider of online and mobile meditation, mindfulness, sleep and movement content in the health & wellness space. We are not a health care or medical device provider, nor should our Products be considered medical advice. Only your physician or other health care provider can do that. While there is third party evidence from research that meditation can assist in the prevention and recovery process for a wide array of conditions as well as in improving some performance and relationship issues, Headspace makes no claims, representations or guarantees that the Products provide a physical or therapeutic benefit.

10.2 Any health information and links on the Products, whether provided by Headspace or by contract from outside providers, is provided simply for your convenience.

10.3 To the extent that you participate in any movement content featured in the Products ("Headspace Move Mode"), you represent and warrant that you are in adequate physical health to perform such activities and have no disability or condition that would make such movement dangerous. You should consult a licensed physician prior to beginning or modifying any exercise program that you undertake, including Headspace Move Mode, especially if you have a prior injury, a history of heart disease, high blood pressure, other chronic illness, or condition. You acknowledge that Headspace has advised you of the necessity of doing so.

10.4 Any advice or other materials in the Products are intended for general information purposes only. They are not intended to be relied upon and are not a substitute for professional medical advice based on your individual condition and circumstances. The advice and other materials we make available are intended to support the relationship between you and your healthcare providers and not replace it. We are not liable or responsible for any consequences of your having read or been told about such advice or other materials as you assume full responsibility for your decisions and actions. In particular, to the fullest extent permitted by law, we make no representation or warranties about the accuracy, completeness, or suitability for any purpose of the advice, other materials and information published as part of the Products.

10.5 There have been rare reports where people with certain psychiatric problems like anxiety and depression have experienced worsening conditions in conjunction with intensive meditation practice. People with existing mental health conditions should speak with their health care providers before starting a meditation practice.

Within the 'Terms & Conditions'

Where to learn more

- FDA Digital Health Center of Excellence
  - New programs & policies
- CDRH Product Databases
  - Existing products that FDA has cleared or approved
  - Decision summaries
- CDRH Division of Industry & Consumer Education (DICE)
  - Specialists in connecting inquiries to the right sources
- Federal Trade Commission
  - Interactive tool on which laws apply
- International Medical Device Regulators Forum (IMDRF)
  - Software as a Medical Device (SaMD) Working Group
- NIH SEED
  - NIH Program Officers can request a consultation between our team and your innovators!

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