Regulation of AL / ML in the US

6.S897/HST.956: Machine Learning for Healthcare

DISCLAIMERS

The opinions and information in this presentation are our own, and do not necessarily reflect the views of the U.S. government or our affiliated institutions.

Regulations and policies are constantly changing. By the time these views have been presented, the information is already old.

Interact early and often with relevant oversight bodies.

Many definitions and frameworks in the health tech industry are in conflict and/or have not yet been created.

Ask questions!

You can be part of the influencers who define and envision the future.

Overview of today's lecture

- Overview US Regulatory Agencies

  A look at the FDA, FTC, FCC and other agencies that have oversight for health-related software and data. With a deeper dive into the newer policies (e.g., software and cybersecurity) coming out of the US FDA.

- How to submit a public comment

  An introduction to how to interact with the US government and influence policy.

- Institutional Review Board (IRBs)

  When to involve the institutional review board (IRB), and how to work with the IRB in digital research.

Before we start, a few examples and use-cases of algorithmically-driven health care products.

Software and algorithms have a wide range of applications

Measure	Diagnose	Treat
With **sensors + algorithms** to create objective measurements	With **advanced algorithms** to support the clinician	With **novel software-based therapies** that may augment or substitute a drug
E.g., Digital biomarkers, clinical decision support	*Digital diagnostics*	*Digital therapeutics*

To develop these products, we'll need to build safe and clinically-validated algorithms.

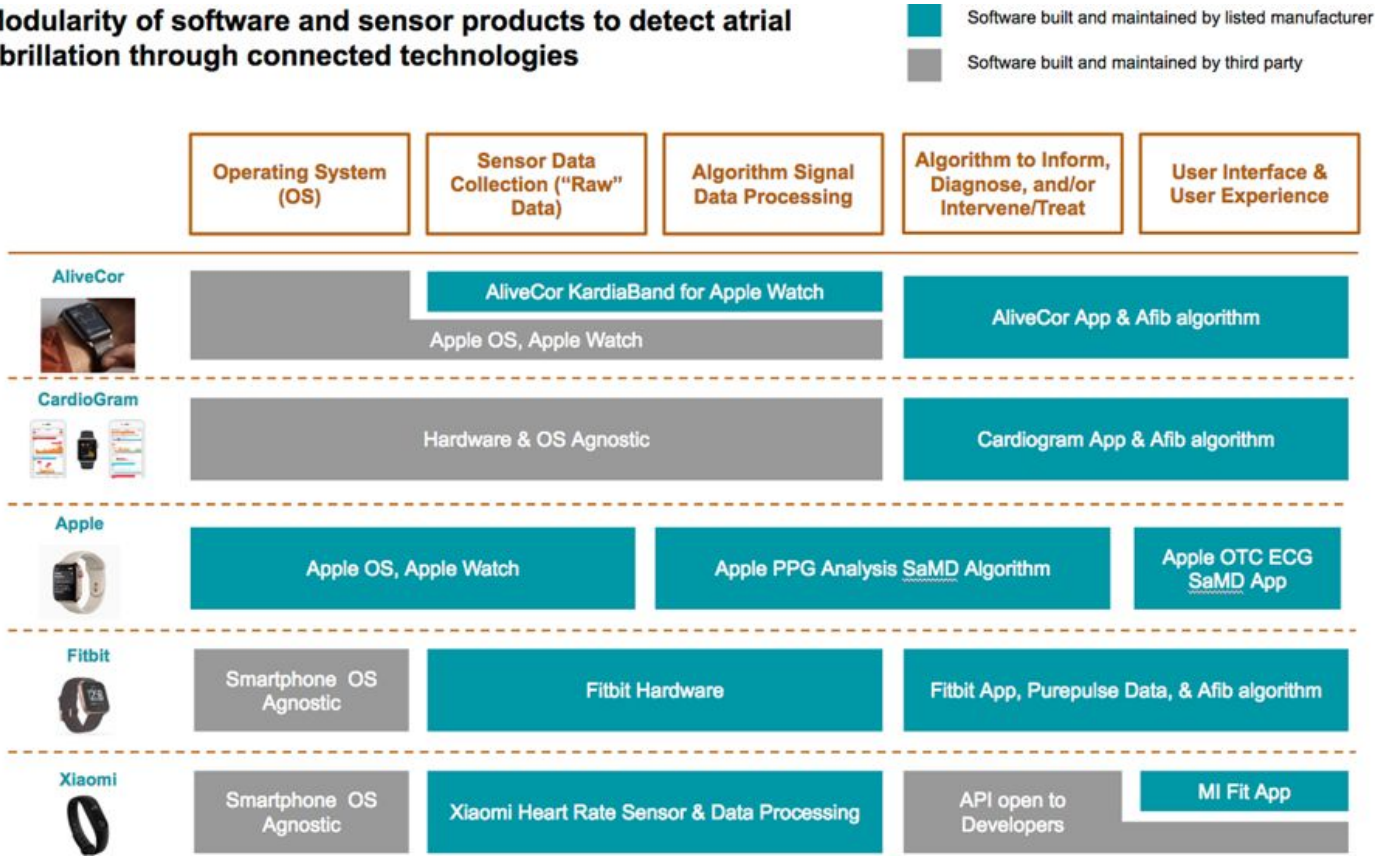
A glossary of terminology and uses of biomarkers and endpoints in biomedical research, medical product development and clinical care

- The BEST framework was created in 2016 by an NIH-FDA Working Group
- Seven types of biomarkers:
  - Diagnostic Biomarker
  - Monitoring Biomarker
  - Pharmacodynamic / Response Biomarker
  - Predictive Biomarker
  - Safety Biomarker
  - Susceptibility / Risk Biomarker

Although not explicitly listed in the BEST framework, a **"digital biomarker"** is a biomarker collected through digital means, often used in a remote (at-home) setting

Source: FDA-NIH BEST Framework, https://www.ncbi.nlm.nih.gov/books/NBK326791/
This image is in the public domain.

Modularity of software and sensor products to detect atrial fibrillation through connected technologies



Source: Coravos A, Khozin S, Mandl KD. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. NPJ Digit Med. 2019;2(1), https://www.nature.com/articles/s41746-019-0090-4

In 2014, AliveCor brought the EKG home…

Philips Pagewriter Touch Interpretive EKG Machine: $15k

Take a medical-grade EKG in just 30 seconds. Results are delivered right to your smartphone.

FDA

Meet Kardia Mobile. Your personal EKG: $99. FDA-Cleared.

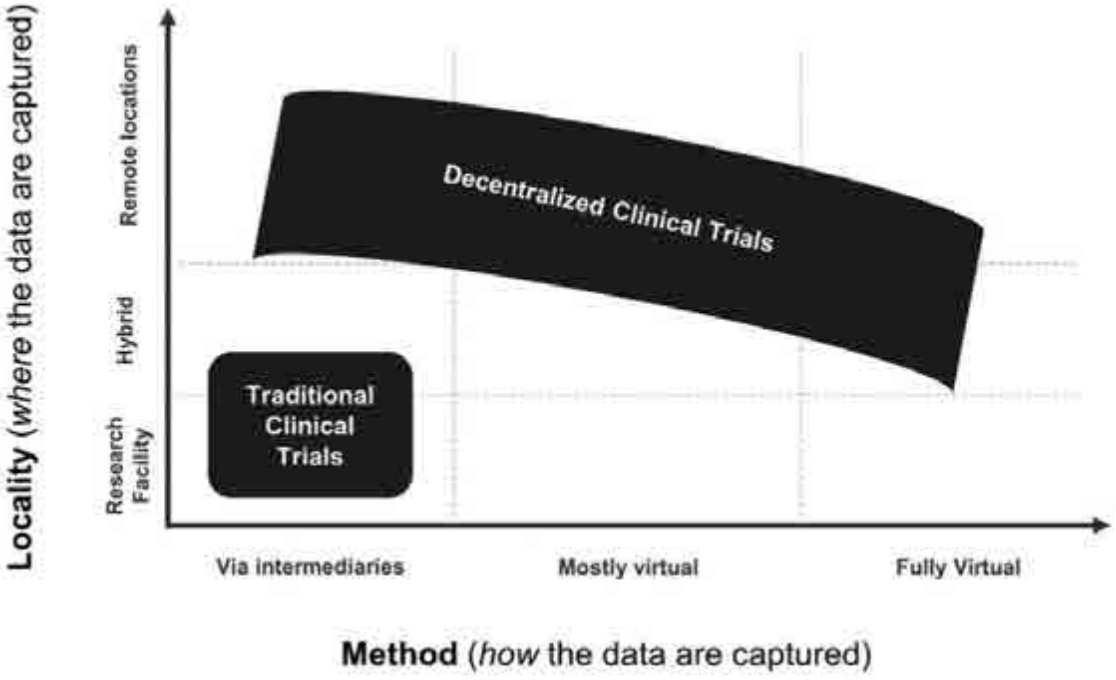
… and since then, the FDA has cleared multiple "software-as-a-medical-device" (SaMDs)

- Developed in a lab at UCSF
- Published in Nature in 2013 and found that video game training enhances cognitive control in older adults
- Technology licensed to Akili Interactive Labs, a start-up, working to commercialize the product

Four Years Later…

Company	FDA Approval	Indication
Aidoc	August 2018	CT Brain bleed diagnosis
iCAD	August 2018	Breast density via mammography
Zebra Medical	July 2018	Coronary calcium scoring
Bay Labs	June 2018	Echocardiogram EF determination
Neural Analytics	May 2018	Device for paramedic stroke diagnosis
IDx	April 2018	Diabetic retinopathy diagnosis
Icometrix	April 2018	MRI brain interpretation
Imagen	March 2018	X-ray wrist fracture diagnosis
Viz ai	February 2018	CT Stroke diagnosis
Arterys	February 2018	Liver and lung cancer (MRI,CT) diagnosis
MaxQ-AI	January 2018	CT Brain bleed diagnosis
Alivecor	November 2017	Atrial fibrillation detection via Apple Watch
Arterys	January 2017	MRI heart interpretation

[1] https://twitter.com/ericTopol/status/1028642832171458563?lang=en
[2] https://www.mobihealthnews.com/content/roundup-12-healthcare-algorithms-cleared-fda



This image is in the public domain. Source: Khozin S, Coravos A. Decentralized Trials in the Age of Real-World Evidence and Inclusivity in Clinical Investigations. Clin Pharmacol Ther. 2019; https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1441

Mobile technologies are enabling new clinical investigation designs like **Decentralized Clinical Trials** (DCTs)

Source: https://www.fda.gov/news-events/speeches-fda-officials/breaking-down-barriers-between-clinical-trials-and-clinical-care-incorporating-real-world-evidence Image is in the public domain.

Digital tools are not making it easy to adhere to historical distinctions between the intervention and measurement/endpoint collection

Software's Purpose	**Clinical Trial Example** *Trial protocol ...*	*Intervention*	*Endpoint data collected by*	Contains Software
Collects a measurement	that collects a digital biomarker	Parkinson's Medication	Smartphone-based tapping test	Opportunity for a clinician to send a patient home to behavioral and psychological measures remotely
Alters the treatment / intervention	with a responsive intervention (e.g., variable dosing)	Insulin Pump	Continuous Glucose Monitor (CGM)	An insulin pump with software that responds/doses based on the CGM reading
Is the treatment / intervention	with a digital therapeutic	Akili Interactive Labs Project:EVO for ADHD	The TOVA test (e.g., change in Attention Performance Index)	Rise of digital therapeutics increases available treatment options for physicians

Digital tools are blurring the line between measuring, diagnosing, and intervening

How does the US ensure that the products brought to market are safe and effective?

US Regulatory Agencies

Different but complementary authorities

The Office of the National Coordinator for Health Information Technology

FDA U.S. FOOD & DRUG ADMINISTRATION

Federal Communications Commission

FEDERAL TRADE COMMISSION
PROTECTING AMERICA'S CONSUMERS

Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

US Food and Drug Administration (FDA)

- Assure safety and effectiveness of medical products (e.g., drugs, devices)
- Facilitate medical product innovation
- Expedite patient access to high quality medical products
- Promote and adopt consensus standards

Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

Office of the National Coordinator (ONC)

- Adopt standards, administer certification programs for health information technology (HIT)
- Promote electronic health information exchange
- Promote HIT policy
- Coordinate HHS HIT policy with other relevant federal agencies

Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

Federal Communications Commission (FCC)

- Regulate interstate and international communications by radio, television, wire, satellite and cable
- Establish technical regulations, administer authorizations for equipment to minimize interference potential

Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

Federal Trade Commission (FTC)

Mission

- Prevent business practices that are anticompetitive or deceptive or unfair to consumers
- Enhance informed consumer choice

Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

Both the FTC and FDA oversight is focused on consumer protection

oversee promotion & advertising

oversee promotion & advertising with a public health perspective

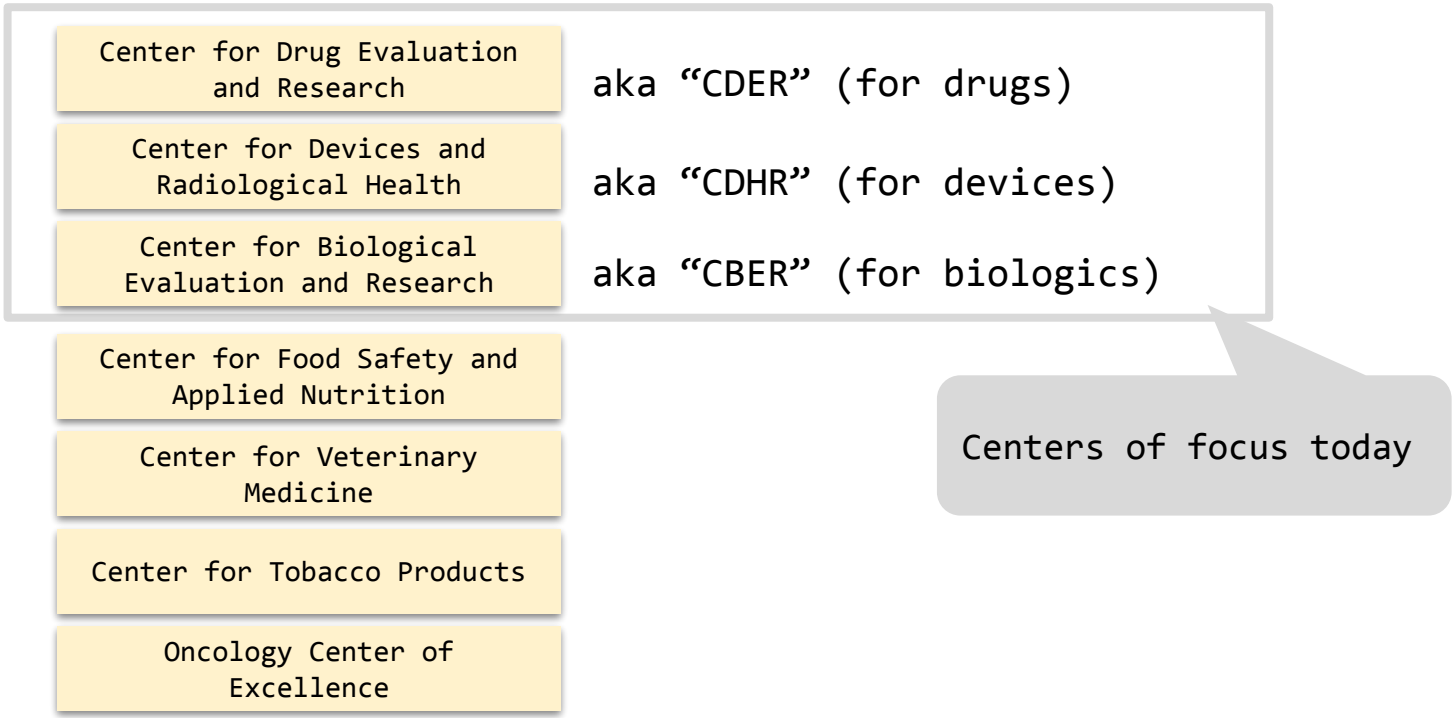
Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

What about National Institute of Standards and Technology (NIST)?

- Non-regulatory federal agency
- Mission: promote innovation & industrial competitiveness
- Involvement in the form of standards for mobile products and software

Source: Mobile Health: Industry Overview and Evolving Regulatory Framework, CERSI, https://cersi.stanford.edu/cersi_mhealth_course

The FDA has multiple Centers, and three are the most relevant to our discussion today

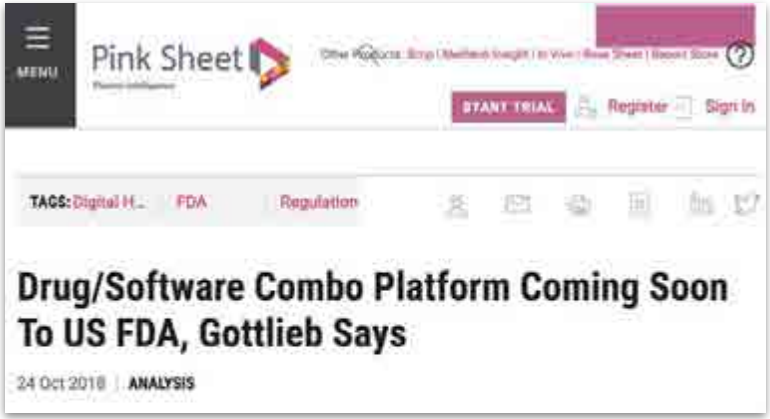


Source: https://www.fda.gov/about-fda/fda-organization-charts/fda-organization-overview

And then came the 21st Century Cures Act, which spurred and authorized FDA innovation around software regulation

- The 21st Century Cures Act (Cures Act), signed into law on December 13, 2016
- Designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.
- Changed definitions and regulations around what is considered to be a “device”

Image is in the public domain.



[1] https://www.federalregister.gov/documents/2018/11/20/2018-25206/prescription-drug-use-related-software-establishment-of-a-public-docket-request-for-comments [2] https://pink.pharmaintelligence.informa.com/PS124134/DrugSoftware-Combo-Platform-Coming-Soon-To-US-FDA-Gottlieb-Says [3] https://www.wired.com/2017/05/medicine-going-digital-fda-racing-catch/

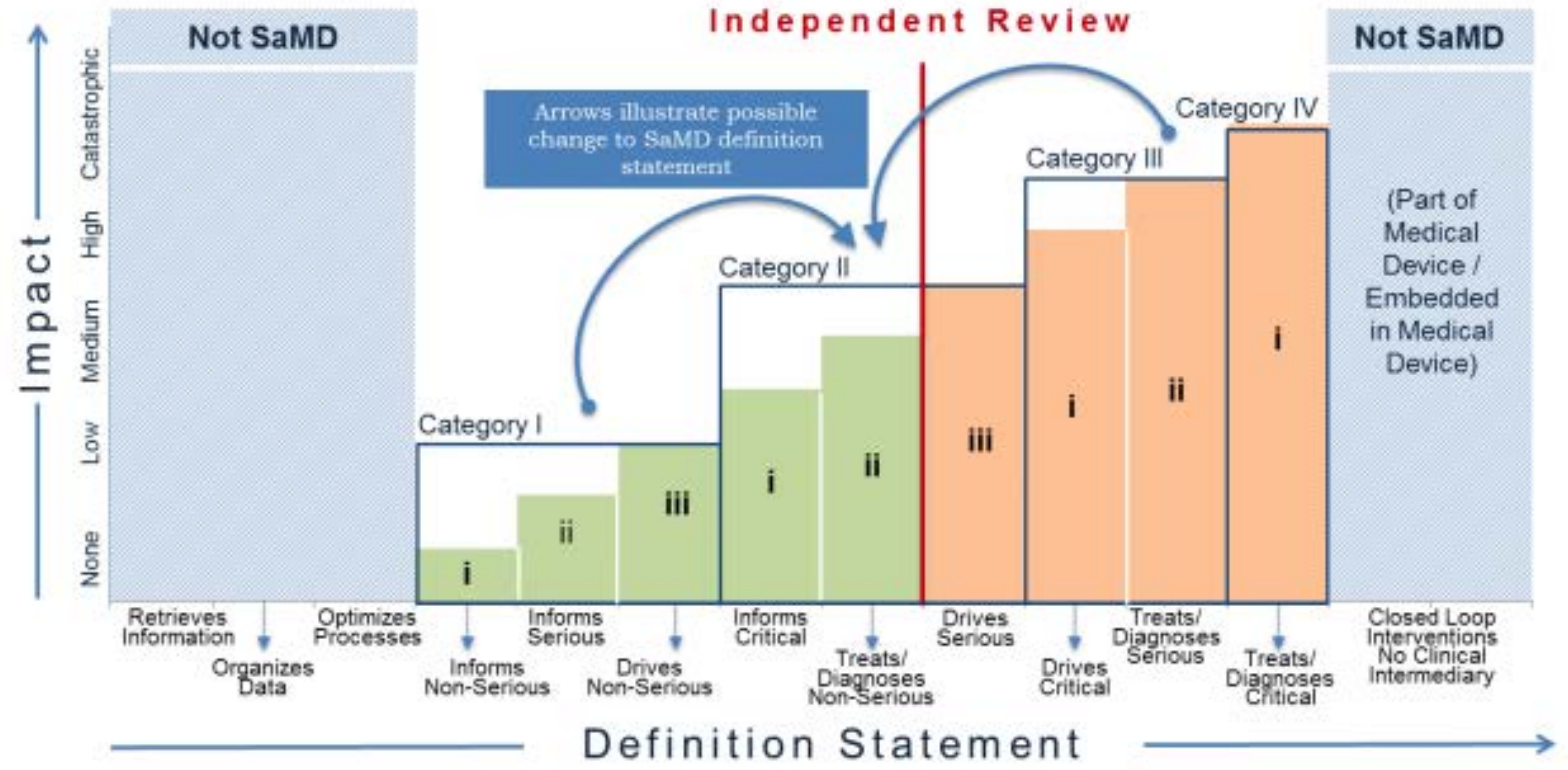
But, what is a medical device?

The FDA defines a medical device as

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- **intended for use** in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Source: https://www.fda.gov/industry/regulated-products/medical-device-overview#What%20is%20a%20medical%20device

Source: http://www.imdrf.org/workitems/wi-samd.asp



Courtesy of FDA. This image is in the public domain.

A “device” is a Term of Art at the FDA

(Try to minimize using the term “device” unless the product is actually a device.)

Is my product a “device”?

Talk with your regulator and lawyer!

The next example is metaphorical rather than factual.

Device?

Not a device?

Device?

Not a device?

Trick question.

It’s all about what the manufacturer claims the product can do.

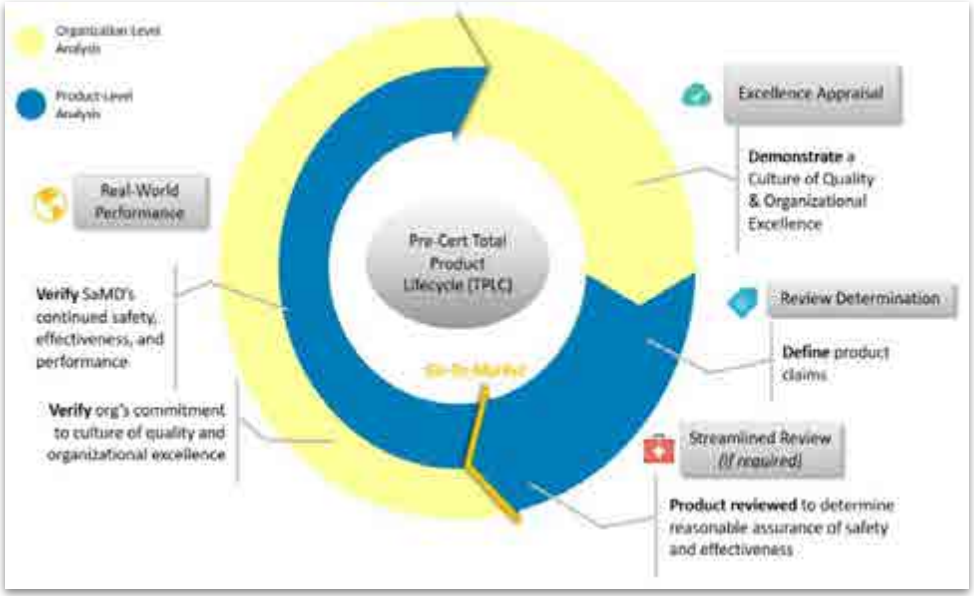
The exact same product can be developed and marketed either as a “device” (and thus, regulated) or not as a “device” (and unregulated) **simply through a change of words, and no change in hardware or code.**

Asking “is my digital product a medical device?” is not the most useful question.

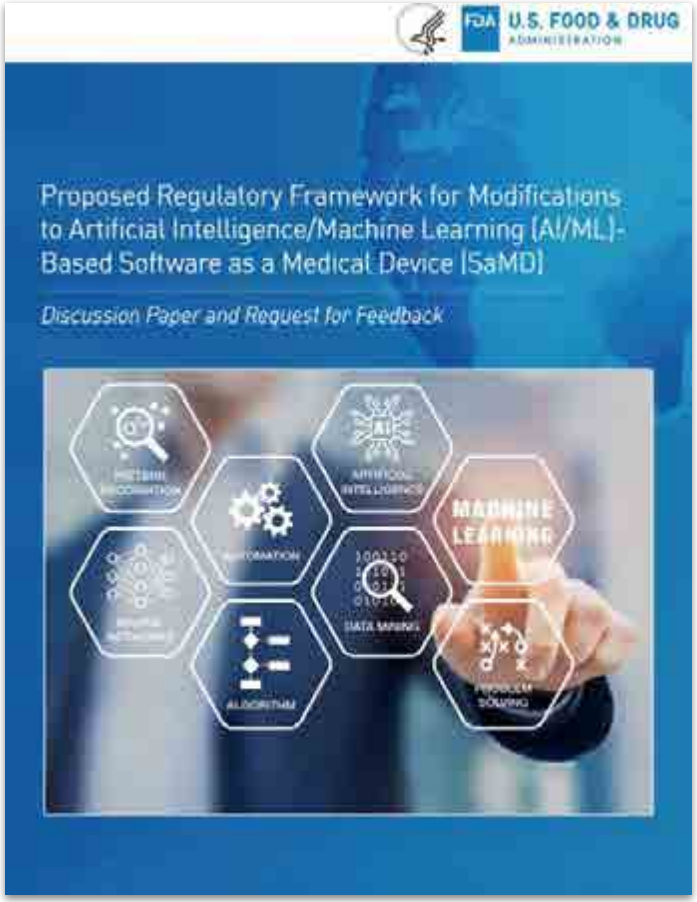
A better question would: “what is the **intended use** of the product?”

(i.e. is the organization making a **medical device claim**?)

US Government work. Image is in the public domain.



Hot off the presses: The most recent version of FDA's Pre-Cert program launched in January 2019. **This program is in the planning phase (pilot).**



This past month the FDA's Digital Health Unit issued a draft discussion paper on modifications for AI/ML-based SaMDs

Source: https://www.regulations.gov/document?D=FDA-2019-N-1185-0001 Image is in the public domain.

FDA-Cleared
!=
FDA-Approved

Regulatory Pathways for Device Development

Regulatory Pathway	**510k**	**De Novo**	**Premarket Approval**
Product risk levels	Class I and II	Class I and II	Class III
FDA decision type	Cleared	Granted	Approved
Requires a predicate	Yes	No	No
Decision criteria	Product demonstrates ‘substantial equivalence’ to a predicate (e.g., no independent assessment of the product required)	Probable benefits of the product outweigh probable risks	Requires independent assessment of the product’s safety and effectiveness

Source: Karger Digital Biomarkers, “Digital Medicine: A Primer on Measurement” (May 2019)

Ok, so the tools are safe and effective -- but what about the information collected from the tools?

WSJ

JOURNAL REPORTS: TECHNOLOGY

The 'Internet of Bodies' Is Here. Are Courts and Regulators Ready?

A network of smart devices attached to or implanted in bodies raises a host of legal and policy questions

By Andrea M. Matwyshyn

Nov. 12, 2018 11:19 a.m. ET

We've all heard of the Internet of Things, a network of products ranging from refrigerators to cars to industrial control systems that are connected to the internet.

Now comes the Internet of Bodies—a network of smart devices that are attached to or inside our bodies. But using the human body as a technology platform raises a host of challenging legal and policy questions that regulators and

Our healthcare system has strong protections for patients' biospecimens, like blood or genomic data, but what about our **digital specimens**?

Sources

[1] https://www.wsj.com/articles/the-internet-of-bodies-is-here-are-courts-and-regulators-ready-1542039566 [2] https://www.thelancet.com/journals/landig/article/PIIS2589-7500(19)30001-9/fulltext

There are many agencies that may oversee health tech products, and there are also many gaps in the current regulatory system.

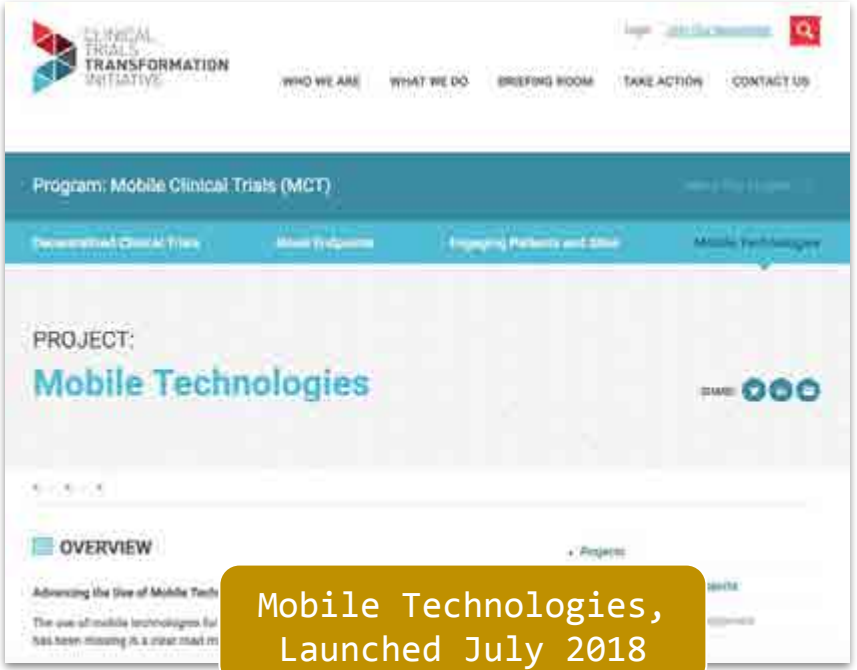
U.S. FOOD & DRUG ADMINISTRATION	Oversees human subjects testing, though many healthy-lifestyle devices fall out of agency's purview (not a "device")
FEDERAL TRADE COMMISSION PROTECTING AMERICA'S CONSUMERS	Police unfair and deceptive practices; main enforcement for security and privacy - small agency
Federal Communications Commission	Oversees connectivity and net neutrality (e.g., regulating access to the internet)
Consumer Product Safety Commission	Only recently started proposed rulemaking for Internet of things
cfpb Consumer Financial Protection Bureau	Oversees information that's used in background testing and other social evaluations

Source: The 'Internet of Bodies' Is Here. Are Courts and Regulators Ready? (WSJ, Nov 2018, Andrea M. Matwyshyn)
https://www.wsj.com/articles/the-internet-of-bodies-is-here-are-courts-and-regulators-ready-1542039566

Examples of how government agencies have interacted with members of the public to inform guidance on new technologies.

FDA and Duke are collaborating in a public-private partnership with member organizations of the Clinical Trial Transformation Initiative (CTTI)

Novel Endpoints, Launched June 2017



Mobile Technologies, Launched July 2018

[1] https://www.ctti-clinicaltrials.org/projects/novel-endpoints
[2] https://www.ctti-clinicaltrials.org/projects/mobile-technologies

US Government work. Image is in the public domain.

Learn more about the FDA-led initiative at WeHeartHackers.org

[1] https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/public-workshop-content-premarket-submissions-management-cybersecurity-medical-devices-january-29-30 [2] WeHeartHackers.org

JMIR Publications | 20

The Case for a Hippocratic Oath for Connected Medical Devices: Viewpoint

Beau Woods; Andrea Coravos; Joshua David Corman

ABSTRACT

Prior to graduating from medical school, soon-to-be physicians take the Hippocratic Oath, a symbolic declaration to provide care in the best interest of patients. As the medical community increasingly deploys connected devices to deliver patient care, a critical question emerges: should the manufacturers and adopters of these connected technologies be governed by the symbolic spirit of the Hippocratic Oath? In 2016, I Am The Cavalry, a grassroots initiative from the cybersecurity research community, published the first Hippocratic Oath for Connected Medical Devices (HOCMD). Over the past three years, the HOCMD has gained broad support and influenced regulatory policy. We introduce five case studies of the HOCMD in practice, leading to a safer and more effective adoption of connected medical technologies.

[1] https://www.jmir.org/2019/3/e12568/
[2] DiMeSociety.org

Clinicians have professional societies to support their development, e.g., the Society for Neuro-Oncology (SNO).

What exists for those who practice and develop digital medicine products?

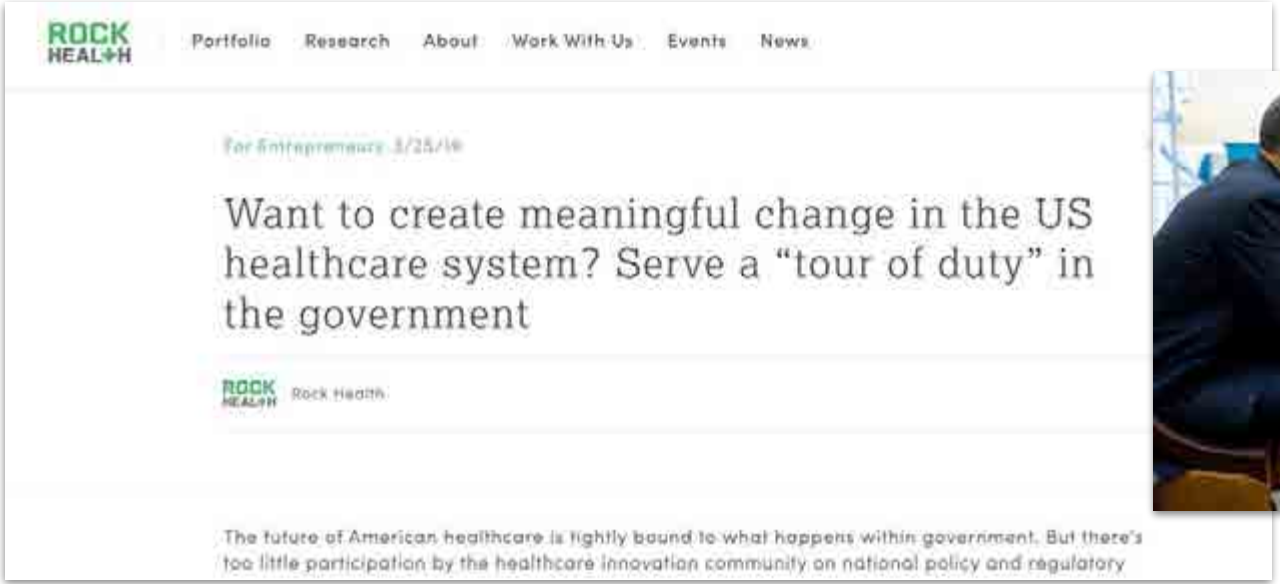
Members from government agencies have teamed up with software engineers, security researchers and more to launch...

DiME

Learn more about the 501(c)3 Digital Medicine (DiME) Society at **DiMeSociety.org**.

How can YOU participate in the US rulemaking process?

Serve a “Tour of Duty”



Source: https://rockhealth.com/create-meaningful-change-in-healthcare-serve-a-tour-of-duty-in-government/

Submit a comment to the public docket

Comments for the FDA AI/ML white paper are due June 3, 2019!

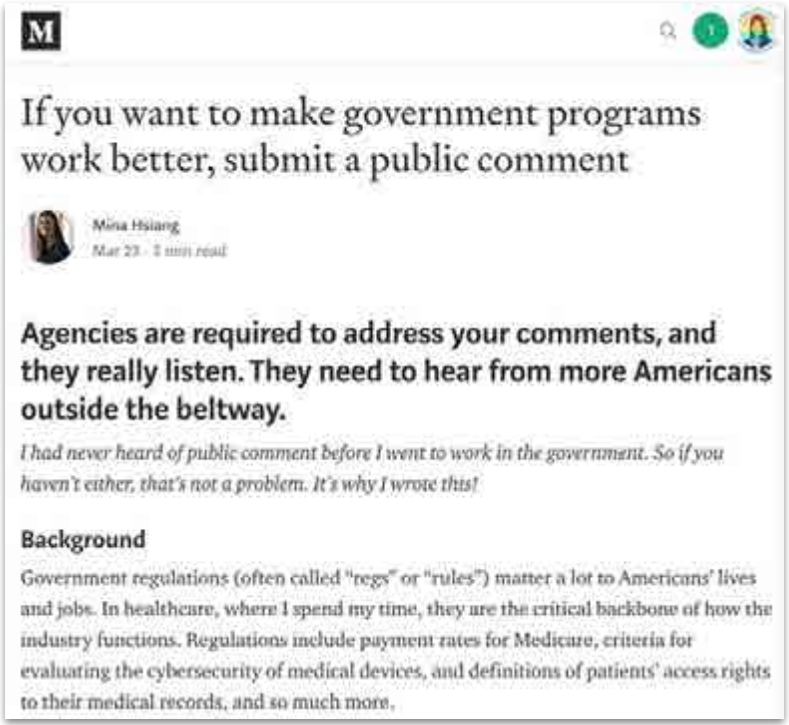
Source: https://www.regulations.gov/document?D=FDA-2019-N-1185-0001

Whenever an agency is proposing either brand-new regulations or changes to existing ones, they must do it in two phases.

1) First the agency will post a draft and ask the public to comment on it

2) Then, they read and digest the comments and draft a final version

Reasons to submit a public comment



If you want to make government programs work better, submit a public comment

Mina Hsiang
Mar 23 · 3 min read

Agencies are required to address your comments, and they really listen. They need to hear from more Americans outside the beltway.

I had never heard of public comment before I went to work in the government. So if you haven't either, that's not a problem. It's why I wrote this!

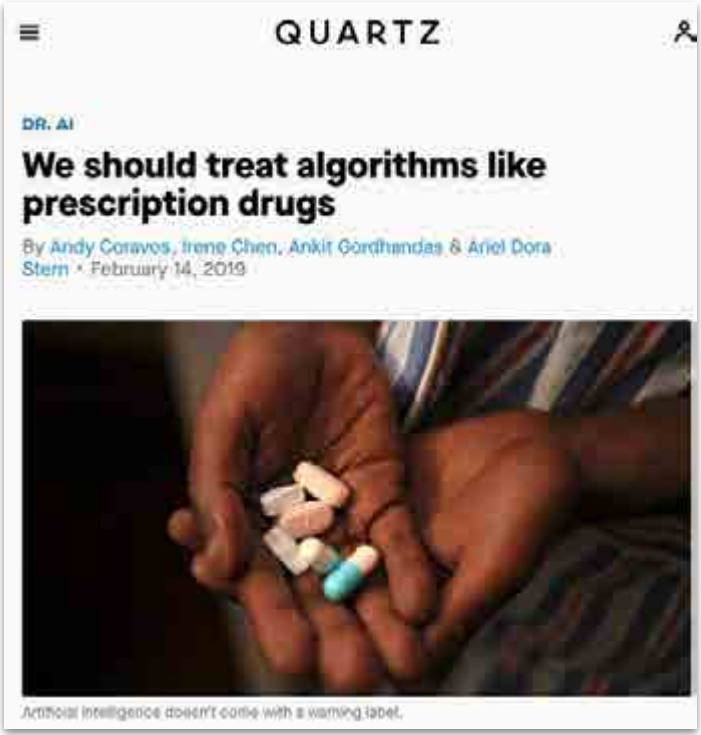
Background

Government regulations (often called "regs" or "rules") matter a lot to Americans' lives and jobs. In healthcare, where I spend my time, they are the critical backbone of how the industry functions. Regulations include payment rates for Medicare, criteria for evaluating the cybersecurity of medical devices, and definitions of patients' access rights to their medical records, and so much more.

- **Anyone can comment.** experts in the field, startups, corporations, lobbying groups, concerned citizens.
- **You will be heard.** Legally, the agency is required to address all comments in the final rule
- **Be a voice from the people.** Major industry players and trade groups almost always submit comments. Meanwhile, there are unfortunately lots of groups who rarely do, like startups, individual doctors, engineers, product managers, security experts, user researchers, and people from families who struggle with the exact scenarios being discussed.

Source: https://medium.com/@mina.h/if-you-have-feedback-on-how-government-programs-can-work-better-you-should-submit-public-comments-22378a934896

Kick around ideas with colleagues to improve the regulatory paradigm. Our society needs new models.



For example, co-authored this op-ed with Irene Chen.

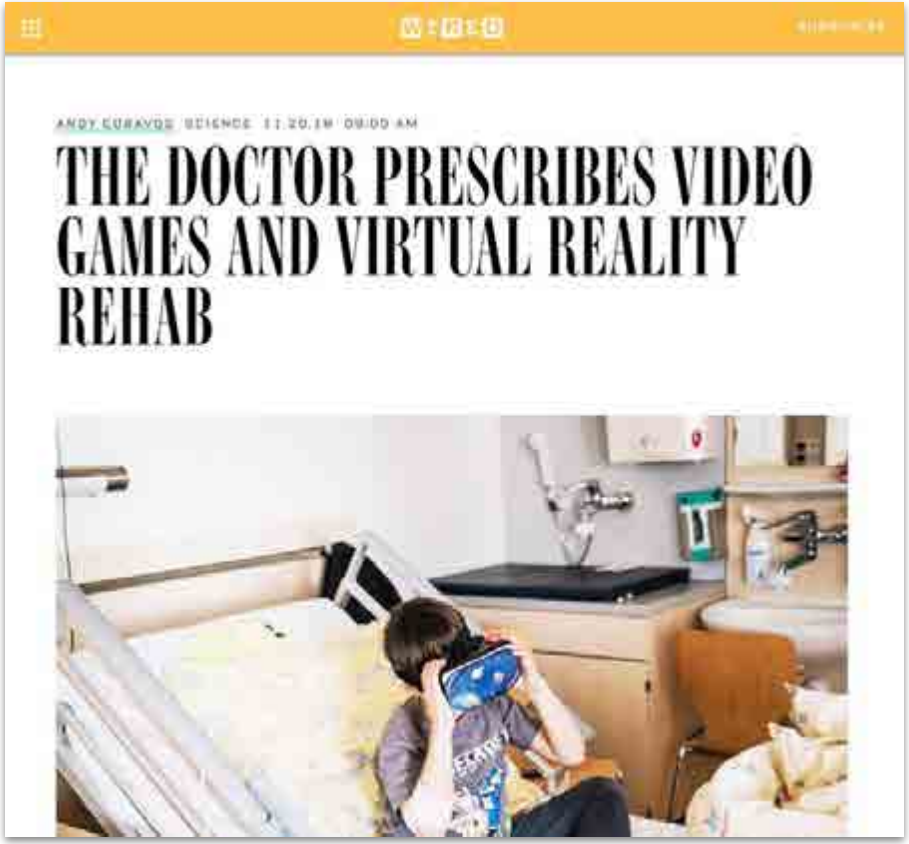
Using **'clinical trials'** frameworks to teach us about AI and algorithm development:

- Designing the **testing protocols** depending on the understanding of the **mechanism of action**
- **Inclusion and exclusion** criteria
- Identifying the "**sponsor**" of the trial
- **Public reporting** of results (e.g., ClinicalTrials.gov)
- Using and adapting existing tools like **informed consent**

Source: https://qz.com/1540594/treating-algorithms-like-prescription-drugs-could-reduce-ai-bias/

While it’s possible you will have to interact with government agencies, it’s even more like you’ll interact with… your IRB.

APPENDIX



ANDY CORAVOS SCIENCE 11.20.18 09:00 AM

THE DOCTOR PRESCRIBES VIDEO GAMES AND VIRTUAL REALITY REHAB

In Nov 2018, WIRED published an op-ed based on the digital medicine framework.

Contained a landscape analysis of software and algorithms that:

- **Measure** health
- **Diagnose**
- **Treat** diseases

… and a perspective on how to bring these products to market safely, effectively and ethically.

Source: WIRED November 2018, https://www.wired.com/story/prescription-video-games-and-vr-rehab/

6.S897 / HST.956 Machine Learning for Healthcare
Spring 2019