Regulation of AL / ML in the US

6.5897/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 defines and envisions 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

<table>
<thead>
<tr>
<th>Measure</th>
<th>Diagnose</th>
<th>Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>With sensors + algorithms to create objective measurements</td>
<td>With advanced algorithms to support the clinician</td>
<td>With novel software-based therapies that may augment or substitute a drug</td>
</tr>
</tbody>
</table>

*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.

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

<table>
<thead>
<tr>
<th>Operating System (OS)</th>
<th>Sensor Data Collection (&quot;Raw&quot; Data)</th>
<th>Algorithm Signal Data Processing</th>
<th>Algorithm to Inform, Diagnose, and/or Intervene/Treat</th>
<th>User Interface &amp; User Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>AliveCor</td>
<td>AliveCor CardioBand for Apple Watch</td>
<td>Apple OS, Apple Watch</td>
<td>AliveCor App &amp; Afib algorithm</td>
<td></td>
</tr>
<tr>
<td>CardioGram</td>
<td>Hardware &amp; OS Agnostic</td>
<td></td>
<td>Cardiogram App &amp; Afib algorithm</td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>Apple OS, Apple Watch</td>
<td>Apple PPG Analysis SaMD Algorithm</td>
<td>Apple OTC ECG SaMD App</td>
<td></td>
</tr>
<tr>
<td>Fitbit</td>
<td>Smartphone OS Agnostic</td>
<td>Fitbit Hardware</td>
<td>Fitbit App, Purepulse Data, &amp; Afib algorithm</td>
<td></td>
</tr>
<tr>
<td>Xiaomi</td>
<td>Smartphone OS Agnostic</td>
<td>Xiaomi Heart Rate Sensor &amp; Data Processing</td>
<td>API open to Developers</td>
<td>MI Fit App</td>
</tr>
</tbody>
</table>

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](https://www.nature.com/articles/s41746-017-0090-4)
In 2014, AliveCor brought the EKG home...

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

Philips Pagewriter Touch Interpretive EKG Machine: $15k


... 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
The FDA approvals for #AI in medicine are accelerating.

@US_FDA @aidocmed @ZebraMedVision @baylabsinc @NeuralAnalytics @icometrix @Viz_AI @ArterysInc @maximumqai @AliveCor imagen.ai eyediagnosis.net

now ≥ 1/month; 10/13 scans, 1 eye disease, 1 neuro, 1 heart

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

Roundup: 12 healthcare algorithms cleared by the FDA

As AI cements its role in healthcare, more and more intelligent software offerings are pursuing 510(k) and De Novo approvals.

By Dave Muoio
November 15, 2018

[2] https://www.mobihealthnews.com/content/roundup-12-healthcare-algorithms-cleared-fda
Mobile technologies are enabling new clinical investigation designs like Decentralized Clinical Trials (DCTs).

SPEECH

Breaking Down Barriers Between Clinical Trials and Clinical Care: Incorporating Real World Evidence into Regulatory Decision Making

JANUARY 28, 2019

Speech by
Scott Gottlieb, M.D.
Commissioner of Food and Drugs - Food and Drug Administration

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

<table>
<thead>
<tr>
<th>Software’s Purpose</th>
<th>Clinical Trial Example</th>
<th>Endpoint data collected by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collects a measurement</td>
<td>Parkinson’s Medication</td>
<td>Smartphone-based tapping test</td>
</tr>
<tr>
<td>Alters the treatment / intervention</td>
<td>Insulin Pump</td>
<td>Continuous Glucose Monitor (CGM)</td>
</tr>
<tr>
<td>Is the treatment / intervention</td>
<td>Akili Interactive Labs Project:EVO for ADHD</td>
<td>The TOVA test (e.g., change in Attention Performance Index)</td>
</tr>
</tbody>
</table>

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

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

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

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

Federal Trade Commission (FTC)

Mission

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

Both the FTC and FDA oversight is focused on consumer protection

oversee promotion & advertising

oversee promotion & advertising with a public health perspective

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

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

- **Center for Drug Evaluation and Research**
  aka “CDER” (for drugs)

- **Center for Devices and Radiological Health**
  aka “CDHR” (for devices)

- **Center for Biological Evaluation and Research**
  aka “CBER” (for biologics)

Centers of focus today:

- **Center for Food Safety and Applied Nutrition**
- **Center for Veterinary Medicine**
- **Center for Tobacco Products**
- **Oncology Center of Excellence**

Source: [https://www.fda.gov/about-fda/fda-organization-charts/fda-organization-overview](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”
Prescription Drug-Use-Related Software; Establishment of a Public Docket; Request for Comments

A Notice by the Food and Drug Administration on 11/20/2018

AGENCY:
Food and Drug Administration, HHS.

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](https://www.fda.gov/industry/regulated-products/medical-device-overview#What%20is%20a%20medical%20device)
Software as a Medical Device (SaMD)

This work item is now complete. This page has been retained for historical reference.

The charter of the Working Group (WG) is to develop guidance that supports innovation and timely access to safe and effective Software as a Medical Device (SaMD) globally. The work is intended to identify commonalities, establish a common vocabulary and develop approaches for appropriate regulatory controls that promote prospective convergence in areas of advanced and innovative technologies in this topic area.

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

FDA-Cleared ≠ FDA-Approved
## Regulatory Pathways for Device Development

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

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

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

Sources
GPS

Fitness tracking app Strava gives away location of secret US army bases

Data about exercise routes shared online by soldiers can be used to pinpoint overseas facilities

Latest: Strava suggests military users ‘opt out’ of heatmap as row deepens

REGULATION

There’s No Such Thing as Anonymous Data

by Scott Berinato
FEBRUARY 08, 2015

Health Insurance Hustle

Your Medical Devices Are Not Keeping Your Health Data to Themselves

CPAP units, heart monitors, blood glucose meters and lifestyle apps generate information that can be used in ways patients don’t necessarily expect. It can be sold for advertising or even shared with insurers, who may use it to deny reimbursement.

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

<table>
<thead>
<tr>
<th>Agency</th>
<th>Responsibilities</th>
</tr>
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<tbody>
<tr>
<td>FDA</td>
<td>Oversees human subjects testing, though many healthy-lifestyle devices fall out of agency’s purview (not a “device”)</td>
</tr>
<tr>
<td>Federal Trade Commission</td>
<td>Police unfair and deceptive practices; main enforcement for security and privacy - small agency</td>
</tr>
<tr>
<td>FCC</td>
<td>Oversees connectivity and net neutrality (e.g., regulating access to the internet)</td>
</tr>
<tr>
<td>Consumer Product Safety Commission</td>
<td>Only recently started proposed rulemaking for Internet of things</td>
</tr>
<tr>
<td>Consumer Financial Protection Bureau</td>
<td>Oversees information that’s used in background testing and other social evaluations</td>
</tr>
</tbody>
</table>

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
Public Workshop - Content of Premarket Submissions for Management of Cybersecurity in Medical Devices January 29-30, 2019

The Food and Drug Administration (FDA) is announcing a public Workshop entitled “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices”. The purpose of the workshop is to discuss the newly released draft guidance Content of Premarket Submissions for Management of Cybersecurity in Medical Devices. FDA seeks to bring together diverse stakeholders to discuss, in-depth, the draft guidance, “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices” and the sub-topic of the draft guidance regarding a Cybersecurity Bill of Materials (CBOM), which can be a critical element in identifying assets, threats, and vulnerabilities.

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

[2] WeHeartHackers.org

Scott Gottlieb, M.D. @SGottliebFDA
Replying to @SGottliebFDA
Workshops like this are one part of our ongoing efforts to bring together all stakeholders in the cybersecurity ecosystem to carry out a “whole of community” approach in which we’re all doing our part to ensure devices are secure and patients are protected.

Scott Gottlieb, M.D. @SGottliebFDA
At future events – like @Defcon – we encourage manufacturers to increase engagement with the cyber research community through device demos and our #wehearthackers event. This demonstrates a company’s commitment to cyber principles: Trustworthiness. Transparency. Resilience.

 несколь dekse dachmecr nerts mnei ofse hteyecy omeit yoh ou tohkel stkaeh onvge tse dbt gudie, “Content of Premarket Submissions for Management of Cybersecurity in Medical Devices” and the sub-topic of the draft guidance regarding a Cybersecurity Bill of Materials (CBOM), which can be a critical element in identifying assets, threats, and vulnerabilities.
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...

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”

Want to create meaningful change in the US healthcare system? Serve a “tour of duty” in the government

The future of American healthcare is tightly bound to what happens within government. But there’s too little participation by the healthcare innovation community on national policy and regulatory

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](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

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