U.S. FOOD & DRUG ADMINISTRATION

AI in Therapeutic Development

A Policy Perspective

M. Khair ElZarrad

Deputy Director
Office of Medical Policy
Center for Drug Evaluation and Research

The views and opinions expressed in the following slides are those of the presenter and may not reflect the views and opinions of the U.S. FDA or HHS. Mentions are not endorsements.

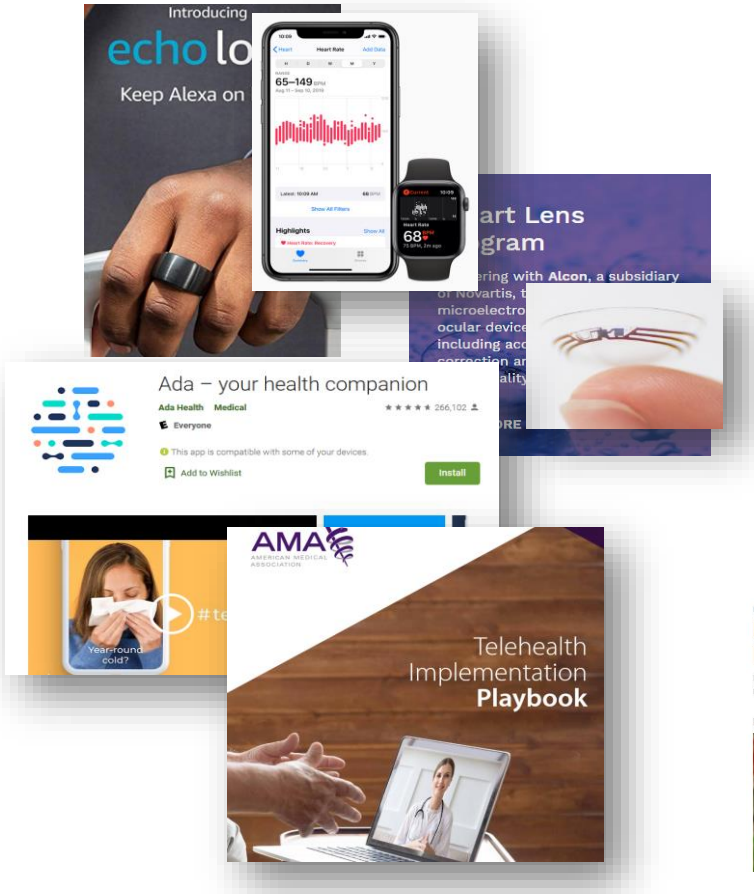
No conflicts to declare & Mentions are not endorsements

Main points

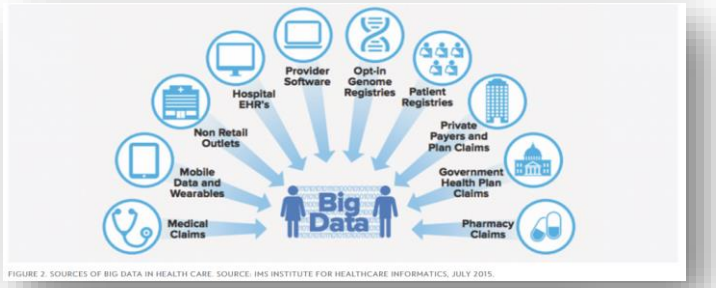
- **The Changing Ecosystem**
- **AI Utilization Across Therapeutic Areas**
- **Policy and Operational implications**
- **Conclusion and next steps**

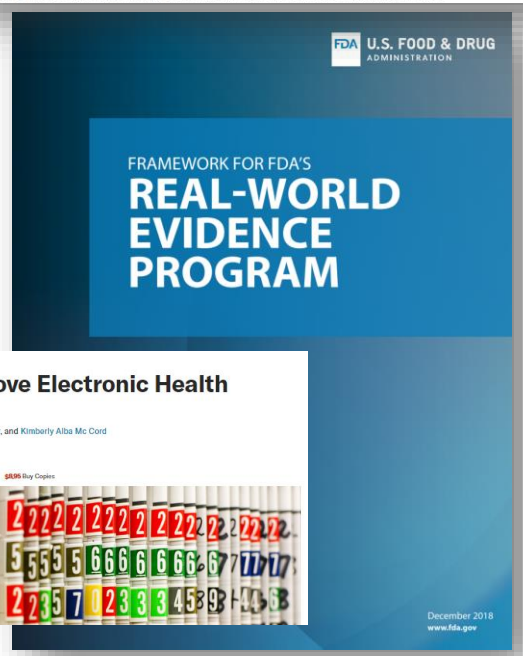
AI is an integral part of a rapidly evolving ecosystem

Increasingly Digital World*



Advancing Evidence Generation Paradigm*





Innovative Clinical Trial Designs*

* Examples – not fully inclusive

AI & Medical Devices

FDA Authorizes Marketing of First Device that Uses Artificial Intelligence to Help Detect Potential Signs of Colon Cancer

Medical device aids clinicians in detecting potential irregularities during colon cancer screening and surveillance

Share | Tweet | Linkedin | Email | Print

For Immediate Release: April 09, 2021

FDA NEWS RELEASE

FDA Authorizes Marketing of First Cardiac Ultrasound Software That Uses Artificial Intelligence to Guide User

Share | Tweet | Linkedin | Email | Print

For Immediate Release: February 07, 2020

FDA NEWS RELEASE

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

Share | Tweet | Linkedin | Email | Print

For Immediate Release: April 11, 2018

npj | Digital Medicine

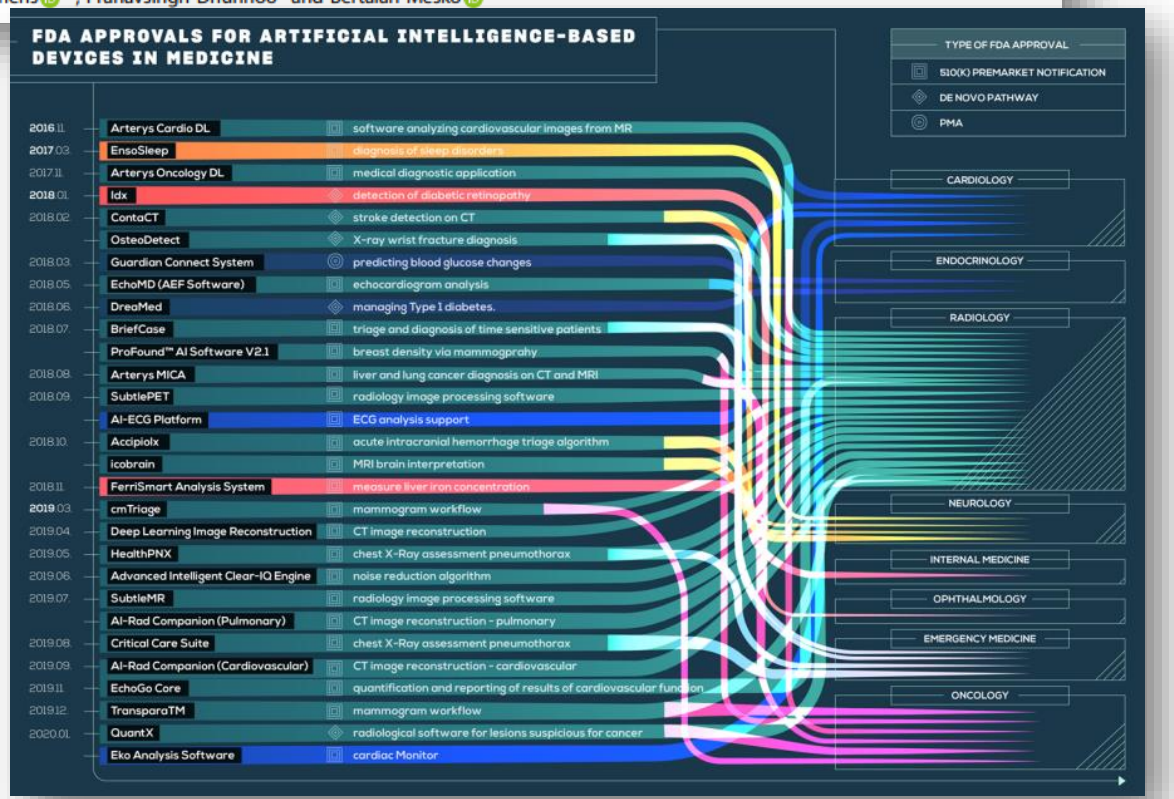
www.nature.com/npjdigitalmed

ARTICLE OPEN

Check for updates

The state of artificial intelligence-based FDA-approved medical devices and algorithms: an online database

Stan Benjamens[1,2], Pranavsingh Dhunnoo[3] and Bertalan Meskó[3,4]✉



https://www.nature.com/articles/s41746-020-00324-0.pdf
https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-device-uses-artificial-intelligence-help-detect-potential-signs-colon
https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye
https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-cardiac-ultrasound-software-uses-artificial-intelligence-guide-user

Going Beyond The Hype – Where We See AI in Action*

Early development
basic science and pre-clinical

- Pathogenesis
- Biomarker identification
- PK/PD modeling
- Compound identification
- Compound screening/design

Clinical Development

- Recruitment and retention
- Adherence and compliance
- Facilitating the use of RWD
- Clinical trial monitoring
- Safety monitoring

Post market

- Identification of long-term safety trends
- Utilization as a part of care
- Continuous monitoring of safety and effectiveness.


Trends in Pharmacological Sciences

CellPress REVIEWS

Special Issue: Rise of Machines in Medicine

Review

Advancing Drug Discovery via Artificial Intelligence

H.C. Stephen Chan,[1,2] Hanbin Shan,[3] Thamani Dahoun,[2,4] Horst Vogel,[2,4] and Shuguang Yuan[1,2]


Trends in Pharmacological Sciences

CellPres REVIE

Special Issue: Rise of Machines in Medicine

Review

Artificial Intelligence for Clinical Trial Design

Stefan Harrer,[1,*] Pratik Shah,[2] Bhavna Antony,[1] and Jianying Hu[3]


ARTICLE

Check for updates

Innovation in Pharmacovigilance: Use of Artificial Intelligence in Adverse Event Case Processing

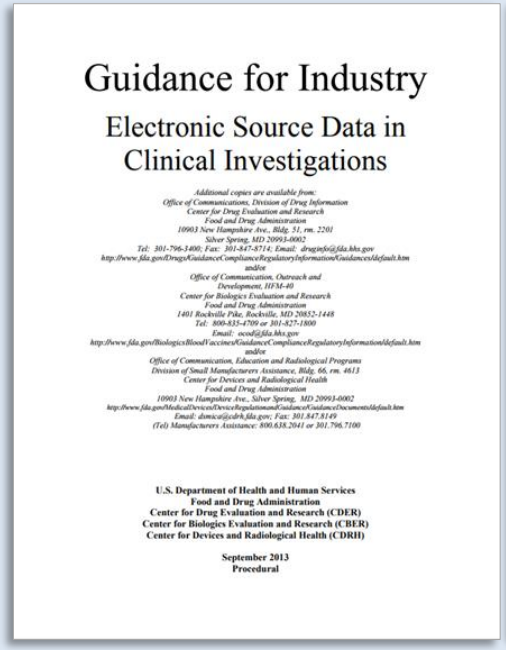
Juergen Schmider[1,*], Krishan Kumar[2], Chantal LaForest[3], Brian Swankoski[4], Karen Naim[5] and Patrick M. Caubel[6]

AI will have an impact across sectors and across therapeutic types

*Examples of potential utility

FDA will Continue to Respond to an Increasingly Digital World

eSource



Guidance for Industry

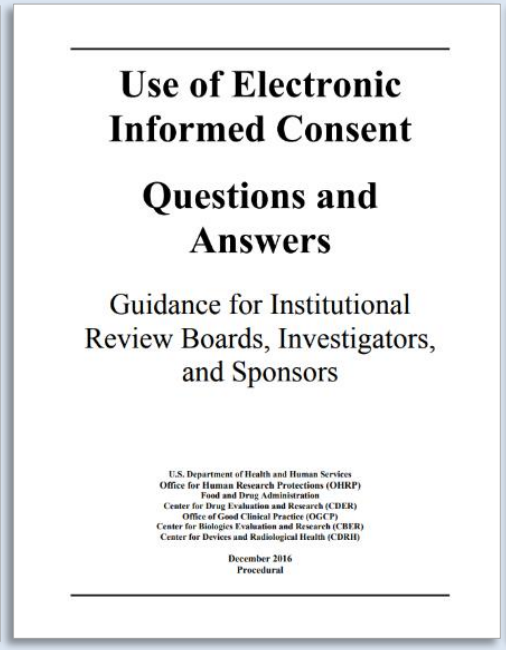
Electronic Source Data in Clinical Investigations

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

September 2013
Procedural

2013

E-Informed Consent



Use of Electronic Informed Consent Questions and Answers

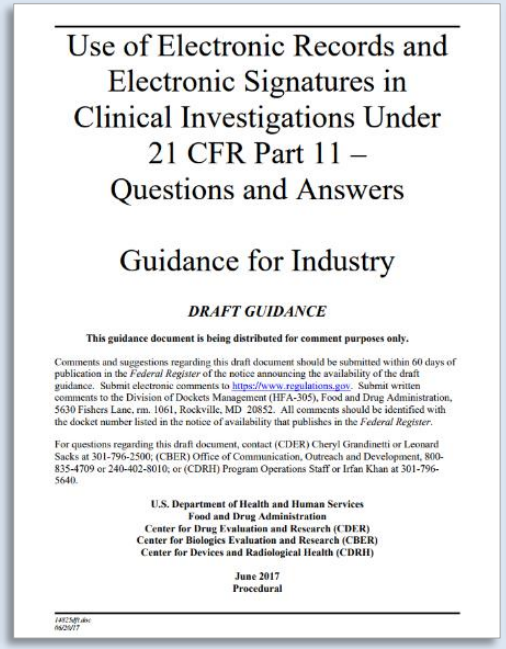
Guidance for Institutional Review Boards, Investigators, and Sponsors

U.S. Department of Health and Human Services
Office for Human Research Protections (OHRP)
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2016
Procedural

2016

E-Records & e-Sig



Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

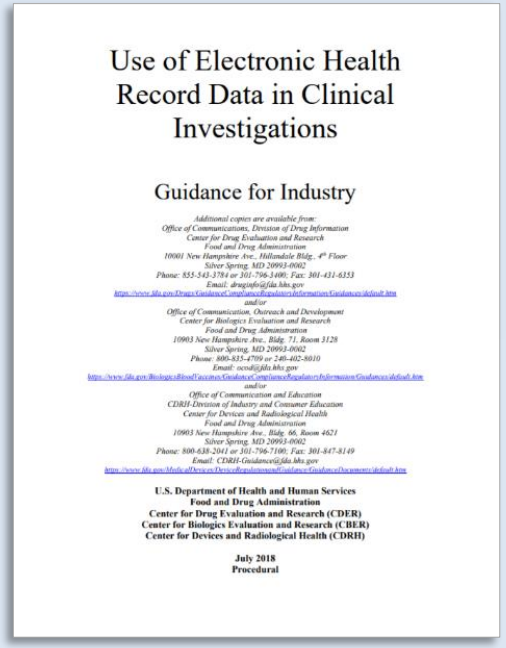
This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2017
Procedural

2017

EHR



Use of Electronic Health Record Data in Clinical Investigations

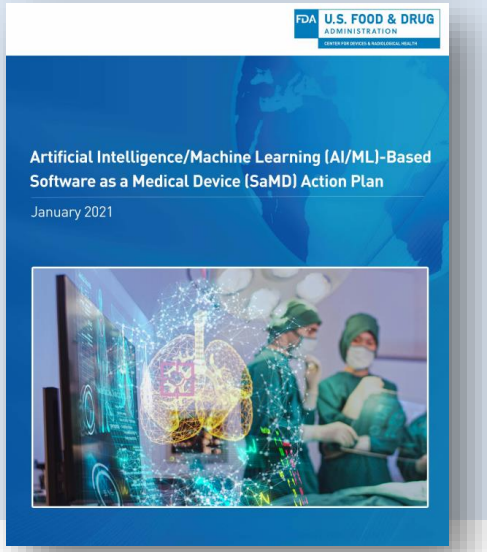
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

July 2018
Procedural

2018

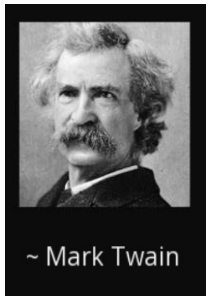
Discussion paper - April 2019



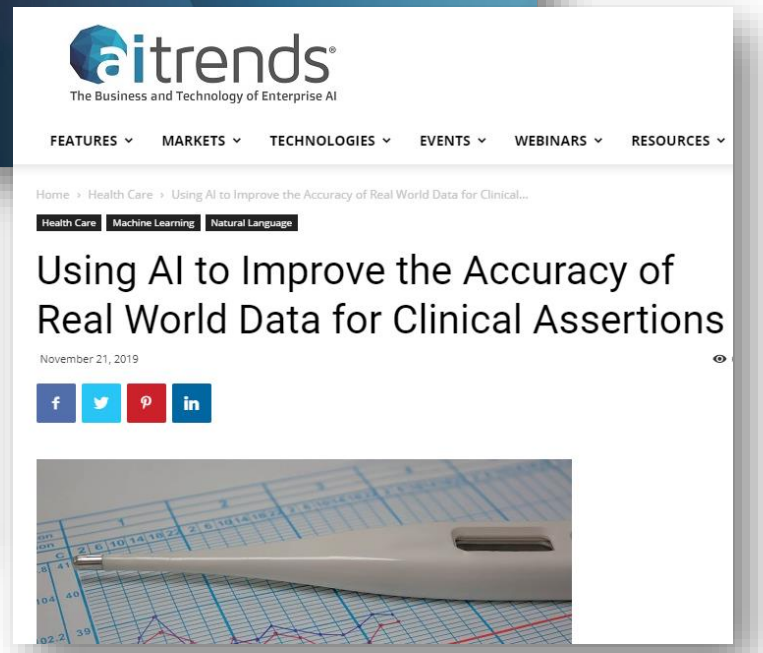
Action plan – Jan 2021

RWD-RWE
Challenges & Opportunities

- **Good news:**
  - 96% of hospitals utilizing EHR
- **Bad news:**
  - Variable EHR systems >700 vendors
  - Routinely don't talk to one another, transferring medical data via fax and CD-ROM
  - Critical or time-sensitive information routinely gets buried in an endless scroll of data . . . — and amid the maze of pulldown menus — it can be missed



In the real world, nothing happens at the right place at the right time . . .



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6659652/pdf/41746_2019_Article_148.pdf
https://www.aitrends.com/healthcare/using-ai-to-improve-the-accuracy-of-real-world-data-for-clinical-assertions/
https://www.nature.com/articles/s41586-021-03430-5

Understanding the Complexities

"Looking under the hood"

Opinion | Ruth Bader Hat Guy? Let Our Algorithm Choose Your Hallo...

Machine learning has a spooky side. These algorithmically generated Halloween costumes show how artificial intelligence can reinforce human...

nytimes.com

Sometimes, the ways algorithms work can have unexpected and disastrous consequences. In 2013, M.I.T. researchers trained an algorithm that was supposed to figure out how to sort a list of numbers. The humans told the algorithm that the goal was to reduce sorting errors, so the program deleted the list entirely, leaving zero sorting errors. And in 1997, another algorithm was supposed to learn to land an airplane on an aircraft carrier as gently as possible. Instead, it discovered that in its simulation it could land the plane with such huge force that the simulation couldn't store the measurement, and would register zero force instead.

- **Prediction algorithms predict the most likely outcome/decision based on input data - not necessarily the accurate answer.**

- **AI may produce unpredictable or unconventional "solutions".**

https://www.nytimes.com/interactive/2018/10/26/opinion/halloween-spooky-costumes-machine-learning-generator.html

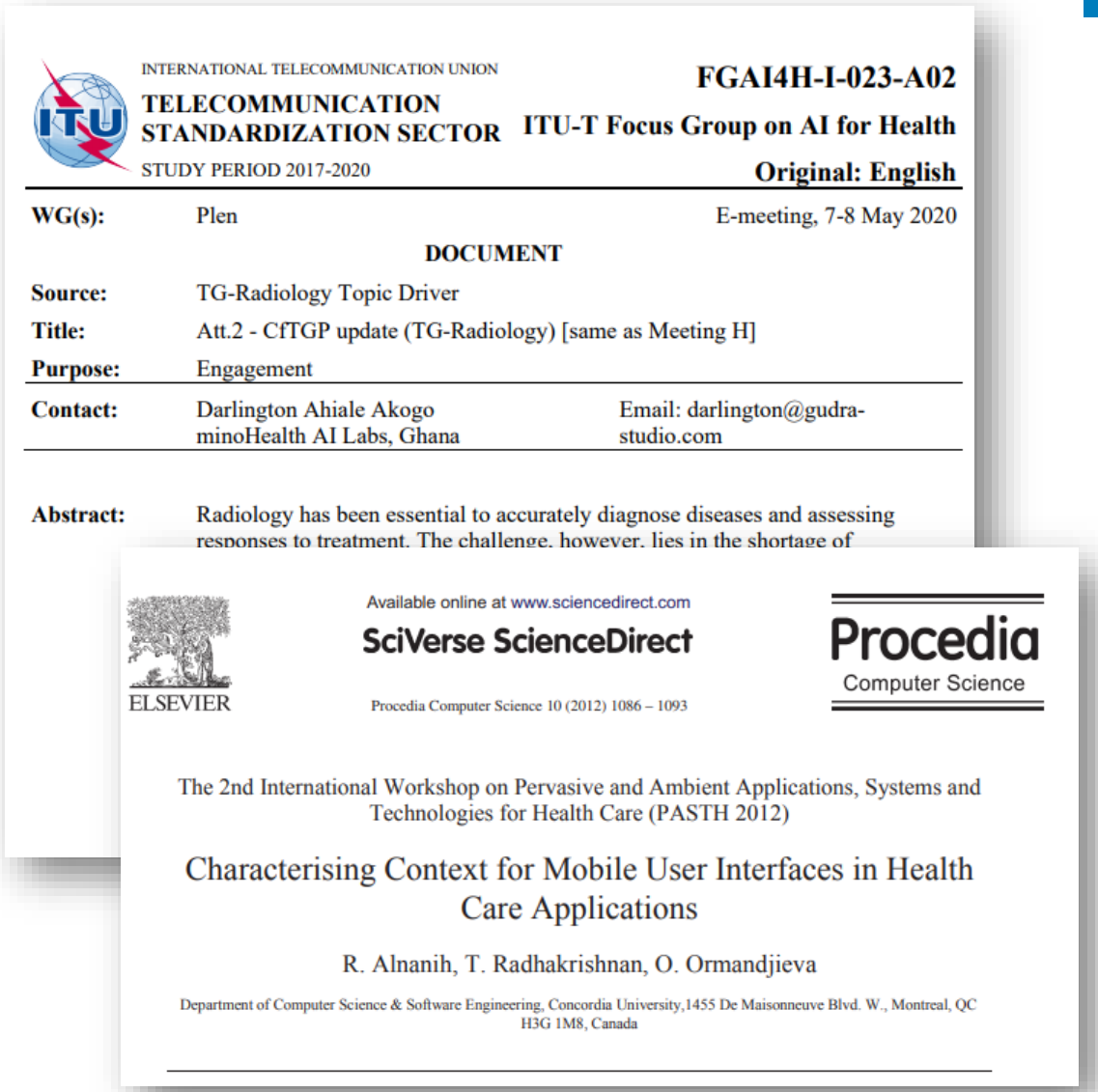
Understanding the Complexities

Benchmarking

- Detecting & managing bias
- Variable standards of care
- Statistical methodologies

The human interface

- Potential behavioral effects
- Perceptions
- Trust



INTERNATIONAL TELECOMMUNICATION UNION
TELECOMMUNICATION STANDARDIZATION SECTOR
STUDY PERIOD 2017-2020

FGAI4H-I-023-A02
ITU-T Focus Group on AI for Health
Original: English

WG(s):	Plen	E-meeting, 7-8 May 2020

DOCUMENT

Source:	TG-Radiology Topic Driver	
Title:	Att.2 - CfTGP update (TG-Radiology) [same as Meeting H]	
Purpose:	Engagement	
Contact:	Darlington Ahiale Akogo minoHealth AI Labs, Ghana	Email: darlington@gudra-studio.com

Abstract: Radiology has been essential to accurately diagnose diseases and assessing responses to treatment. The challenge, however, lies in the shortage of

ELSEVIER

Available online at www.sciencedirect.com
SciVerse ScienceDirect

Procedia Computer Science 10 (2012) 1086 – 1093

Procedia
Computer Science

The 2nd International Workshop on Pervasive and Ambient Applications, Systems and Technologies for Health Care (PASTH 2012)

Characterising Context for Mobile User Interfaces in Health Care Applications

R. Alnanih, T. Radhakrishnan, O. Ormandjieva

Department of Computer Science & Software Engineering, Concordia University,1455 De Maisonneuve Blvd. W., Montreal, QC H3G 1M8, Canada

https://www.itu.int/en/ITU-T/focusgroups/ai4h/Pages/tg.aspx
http://www.skateboardingalice.com/papers/2009_Alnanih.pdf

Transparency, and Documentation

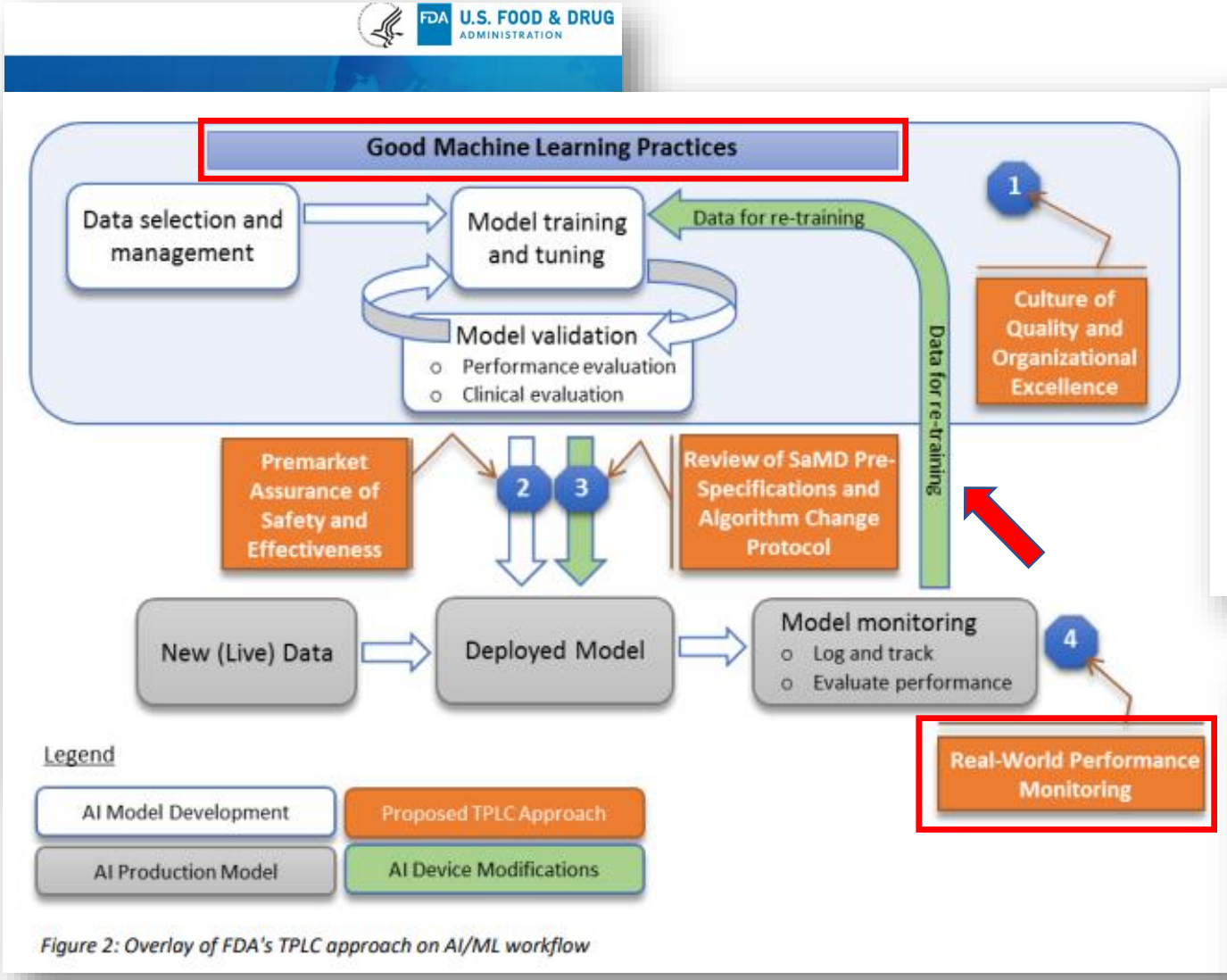


Figure 2: Overlay of FDA's TPLC approach on AI/ML workflow

Special Review

How the FDA Regulates AI

H. Benjamin Harvey, MD, JD, Vrushab Gowda, BS

Recent years have seen digital technologies increasingly leveraged to multiply conventional imaging modalities' diagnostic power. Artificial intelligence (AI) is most prominent among these in the radiology space, touted as the "stethoscope of the 21st century" for its potential to revolutionize diagnostic precision, provider workflow, and healthcare expenditure. Partially owing to AI's unique characteristics, and partially due to its novelty, existing regulatory paradigms are not well suited to balancing patient safety with furthering the growth of this new sector. The current review examines the historic, current, and proposed regulatory treatment of AI-empowered medical devices by the US Food and Drug Administration (FDA). An innovative framework proposed by the FDA seeks to address these issues by looking to current good manufacturing practices (cGMP) and adopting a total product lifecycle (TPLC) approach. If brought into force, this may reduce the regulatory burden incumbent on developers, while holding them to rigorous quality standards, maximizing safety, and permitting the field to mature.

Key Words: Artificial intelligence; FDA; Medical Device; Regulation; Policy; Radiology.

MEDTECHDIVE Deep Dive Library Events

Medical Devices Policy & Regulation Clinical Trials Manufacturing Legal M&A Research

BRIEF

FDA AI-machine learning strategy remains work in progress

https://www.fda.gov/media/122535/download
https://www.medtechdive.com/news/fda-ai-machine-learning-strategy-remains-work-in-progress/585146/
https://pubmed.ncbi.nlm.nih.gov/31818387/

Transparency, and Documentation

CONSENSUS STATEMENT

https://doi.org/10.1038/s41591-020-1034-x

nature medicine

Check for updates

OPEN

Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension

Xiaoxuan Liu[1,2,3,4,5], Samantha Cruz Rivera[5,6,7], David Moher[8,9], Melanie J. Calvert[4,5,6,7,10,11,12], Alastair K. Denniston[2,3,4,5,6,13] ✉ and The SPIRIT-AI and CONSORT-AI Working Group*

- Consolidated Standards of Reporting Trials (CONSORT)
- Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

The CONSORT-AI Extension

&

SPIRIT-AI Extension

AI During Public Health Emergency

FDA Guidance on *Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*

- Technology is key to enable processes, such as remote data capture and monitoring.
- Robust structures and processes for data flow and robust analytics

Contains Nonbinding Recommendations

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on January 27, 2021

For questions on clinical trial conduct during the COVID-19 pandemic, please email Clinicaltrialconduct-COVID19@fda.hhs.gov.

AI Can Help

FIERCE Biotech — BIOTECH COVID-19 RESEARCH CRO MEDTECH

Virtual Events FiercePharma Jobs Resources

MedTech

FDA authorizes first AI-powered armband for COVID-19 screening

by Conor Hale | Mar 22, 2021 10:40am

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-17971-2 OPEN

Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources

Home > Search Results > Study Record Detail

Artificial Intelligence-assisted Diagnosis and Prognostication in COVID-19 Using Electrocardiograms (AI-COV-19)

https://www.fiercebiotech.com/medtech/fda-authorizes-first-ai-powered-armband-for-covid-19-screening
https://www.nature.com/articles/s41467-020-17971-2#:~:text=Preliminary%20studies%20indicate%20chest%20CT,%2C18%2C19%2C20.
https://clinicaltrials.gov/ct2/show/NCT04510441

So, what is the FDA doing?

CDER AI Steering Committee **(AISC)**

Established in 2020

- **Coordination**
- **Education**
- **Facilitation of projects and ideas**
- **Building common understanding**
- **Communication**

Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program

Examples of submissions that might be considered for ISTAND include, but are not limited to:

Tools that may help enable remote or decentralized trials

- Application of patient-performed digital photography in dermatology trials

Tools that may advance our understanding of drugs

- Use of tissue chips (i.e., microphysiological systems) to assess safety or efficacy questions
- Development of novel nonclinical pharmacology/toxicology assays

Tools that leverage digital health technologies

- Use of artificial intelligence (AI)-based algorithms to evaluate patients, develop novel endpoints, or inform study design
- Use of novel digital health technologies (e.g., wearables) for patient assessment

Development programs needed for evaluation of adherence sensors

https://www.fda.gov/medical-devices/digital-health-center-excellence
https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

Key Questions! – what to add?

- What should be the parameters for transparency and documentation?
- What are the needed validation & benchmarking approaches?
- Can our current policies and regulations (and policy development processes) keep up with rapidly evolving innovations?
- What will an effective work force & work processes look like for a robust regulatory agency?
- What are the ethicall implications
  - ❑ Are our IRBs and DSMBs ready?
  - ❑ Informed consent
  - ❑ Data privacy
  - ❑ What about the Human-Machine interface?
- How best to develop new norms, shared understandings, and ultimately standards?
  - ❑ Early engagement with regulatory agencies
  - ❑ Collaborations, feedback, and continued engagement

https://www.statnews.com/2019/11/07/artificial-intelligence-drug-development-fda-standards-needed/
http://nautil.us/issue/66/clockwork/we-need-an-fda-for-algorithms
https://www.sciencedirect.com/science/article/abs/pii/S0277953620303919?via%3Dihub

Economy and Markets, Education, Machine Learning

The 2021 AI Index: Major Growth Despite the Pandemic

This year's report shows a maturing industry, significant private investment, and rising competition between China and the U.S.

Mar 3, 2021 | Jack Clark and Daniel Zhang

TOP 9 TAKEAWAYS

1 AI investment in drug design and discovery increased significantly

"Drugs, Cancer, Molecular, Drug Discovery" received the greatest amount of private AI investment in 2020, with more than USD 13.8 billion, 4.5 times higher than 2019.

2 The industry shift continues

In 2019, 65% of graduating North American PhDs in AI went into industry—up from 44.4% in 2010, highlighting the greater role industry has begun to play in AI development.

3 Generative everything

AI systems can now compose text, audio, and images to a sufficiently high standard that humans have a hard time telling the difference between synthetic and non-synthetic outputs for some constrained applications of the technology.

4 AI has a diversity challenge

In 2019, 45% new U.S. resident AI PhD graduates were white—by comparison, 2.4% were African American and 3.2% were Hispanic.

5 China overtakes the US in AI journal citations

After surpassing the US in the total number of journal publications several years ago, China now also leads in journal citations; however, the US has consistently (and significantly) more AI conference papers (which are also more heavily cited) than China over the last decade.

6 The majority of the US AI PhD grads are from abroad—and they're staying in the US

The percentage of international students among new AI PhDs in North America continued to rise in 2019, to 64.3%—a 4.3% increase from 2018. Among foreign graduates, 81.8% stayed in the United States and 8.6% have taken jobs outside the United States.

7 Surveillance technologies are fast, cheap, and increasingly ubiquitous

The technologies necessary for large-scale surveillance are rapidly maturing, with techniques for image classification, face recognition, video analysis, and voice identification all seeing significant progress in 2020.

8 AI ethics lacks benchmarks and consensus

Though a number of groups are producing a range of qualitative or normative outputs in the AI ethics domain, the field generally lacks benchmarks that can be used to measure or assess the relationship between broader societal discussions about technology development and the development of the technology itself. Furthermore, researchers and civil society view AI ethics as more important than industrial organizations.

9 AI has gained the attention of the U.S. Congress

The 116th Congress is the most AI-focused congressional session in history with the number of mentions of AI in congressional record more than triple that of the 115th Congress.

https://aiindex.stanford.edu/report/

Acknowledgements

- ***Jacqueline Corrigan-Curay***
- ***Rose Purcell***
- ***John Concato***
- ***Karen Boyd***
- ***Leonard Sacks***
- ***Mathew Diamond***