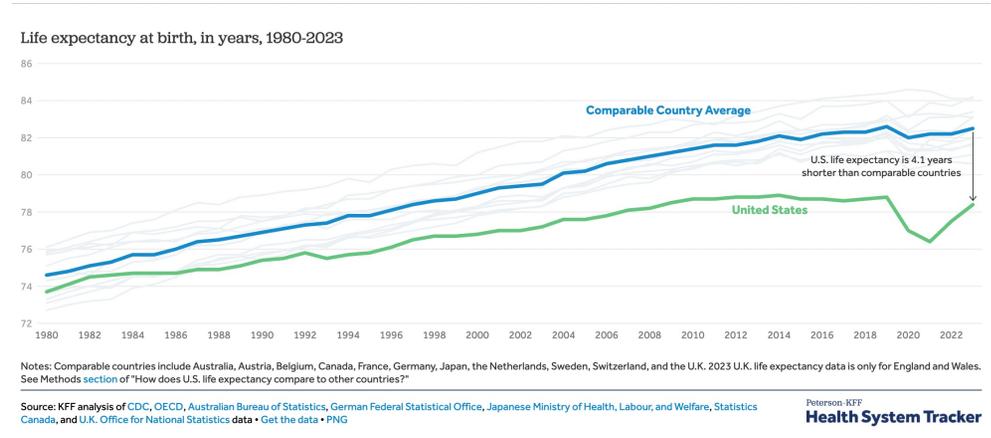# Safety and Efficacy Perspectives in Clinical AI

Shantanu Nundy, MD

Advisor on Artificial Intelligence (Contractor), Office of the Commissioner, FDA

Macro view of the problem

- 100M no routine source of medical care[1]

- 75M in Health Professional Shortage Areas

- Medical error third leading cause of death (250,000 deaths)[2]

- 30M with rare diseases (1 in 10); only 5 percent have approved treatments[3]

- US life expectancy flat/declining and lower than peers[4] (6 in 10 adults with chronic diseases)

Life expectancy at birth, in years, 1980-2023

Notes: Comparable countries include Australia, Austria, Belgium, Canada, France, Germany, Japan, the Netherlands, Sweden, Switzerland, and the U.K. 2023 U.K. life expectancy data is only for England and Wales. See Methods section of "How does U.S. life expectancy compare to other countries?"

Source: KFF analysis of CDC, OECD, Australian Bureau of Statistics, German Federal Statistical Office, Japanese Ministry of Health, Labour, and Welfare, Statistics Canada, and U.K. Office for National Statistics data • Get the data • PNG

Peterson-KFF **Health System Tracker**

https://www.healthsystemtracker.org/chart-collection/u-s-life-expectancy-compare-countries/#Life%20expectancy%20at%20birth,%20in%20years,%201980-2023

AI Across the Drug Product Life Cycle

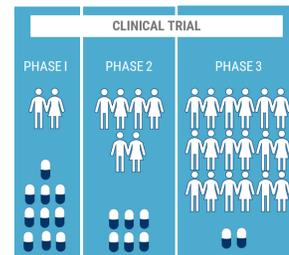| Discovery	Nonclinical Research	Clinical Research	Manufacturing and Postmarket Safety Monitoring
• Drug Target Identification, Selection, and Prioritization • Compound Screening and Design	• PK/PD and toxicologic studies • Dose range finding	• Dose range finding • Site selection • Recruitment and Retention • Adherence • Data collection, management, and analysis • RWD analyses • Clinical endpoint assessment	• Advanced pharmaceutical manufacturing • Post-market safety surveillance or pharmacovigilance (PV)

Image source: cbinsights.com

CDER has received >800 submissions with AI

FDA

Submissions by Therapeutic Area

Oncology: 208
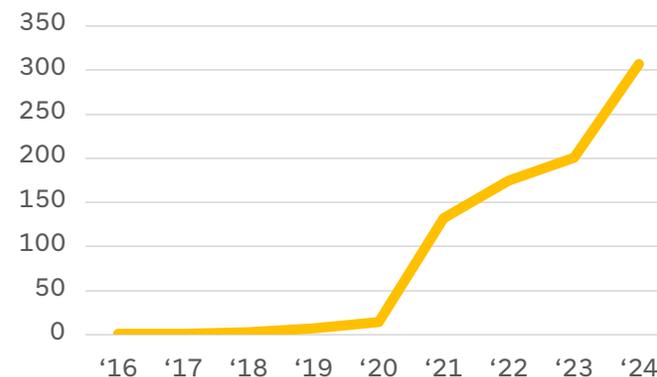Gastroenterology: 104
Neurology: 94
Psychiatry: 79
All other: 356

Number of Submissions (n)
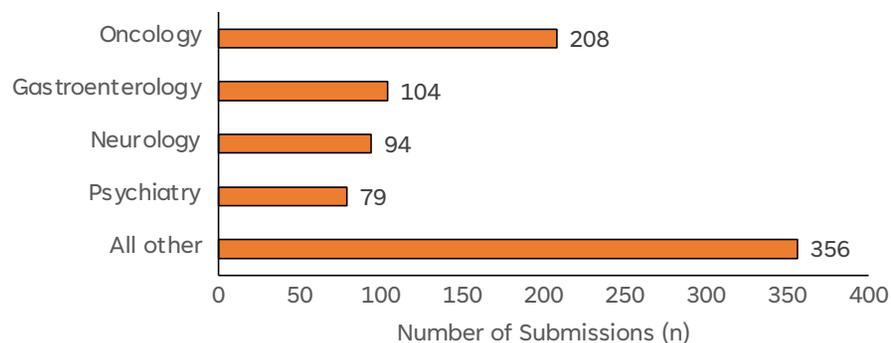
Example Use Cases of AI
- Patient selection
- Outcome prediction
- Confounding adjustment
- Pharmacometric modeling
- Digital Twins, external controls, synthetic controls
- Postmarket safety monitoring

Total Number of Submissions with AI by Year

Submission	Year								
	'16	'17	'18	'19	'20	'21	'22	'23	'24
IND	-	-	2	6	12	128	153	174	248
NDA, ANDA, BLA	1	1	1	1	1	2	22	17	50
DDT, CPIM	-	-	-	-	1	2	-	10	9

Draft Guidance

THE TABLE OF CONTENTS

Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry and Other Interested Parties

DRAFT GUIDANCE

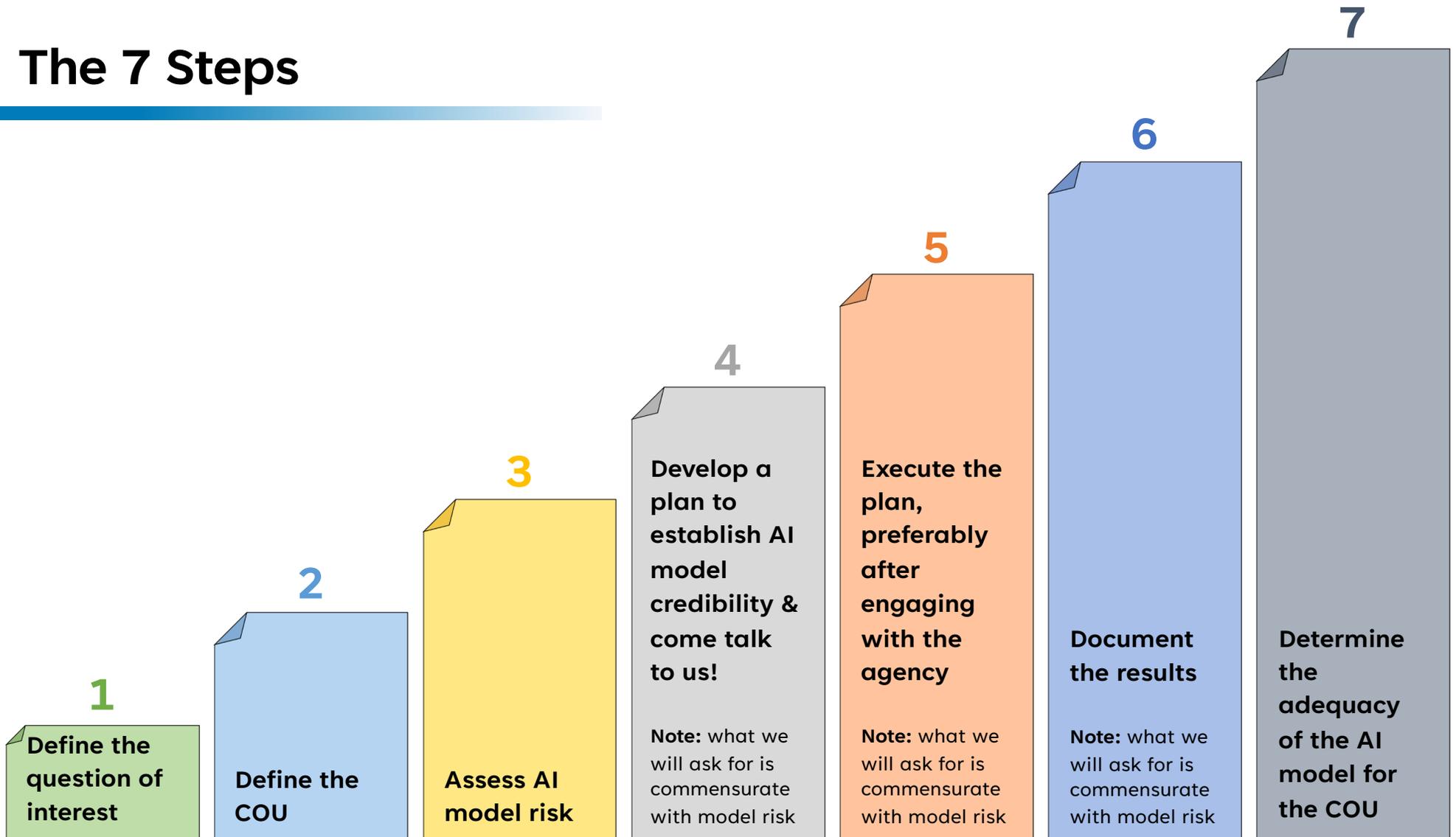This guidance document is being distributed for comment purposes only.

The 7 Steps

1

Define the question of interest

2

Define the COU

3

Assess AI model risk

4

Develop a plan to establish AI model credibility & come talk to us!

Note: what we will ask for is commensurate with model risk

5

Execute the plan, preferably after engaging with the agency

Note: what we will ask for is commensurate with model risk

6

Document the results

Note: what we will ask for is commensurate with model risk

7

Determine the adequacy of the AI model for the COU

Step 3: How do we assess AI model risk?

FDA

Mischaracterization of patients' risk status could result in serious adverse reaction and potentially death

Decision Consequence: HIGH

Model risk HIGH

Model risk MEDIUM

Model risk LOW

Decision Consequence

Model Influence

AI model is the ***only*** determinant of which type of monitoring a patient undergoes

Model Influence: HIGH

GENERAL NOTE: Darker shades indicate greater model risk.

Model risk matrix. The model risk transitions from low to high as decision consequence or model influence increases. The ratings for model influence and decision consequence are determined independently.
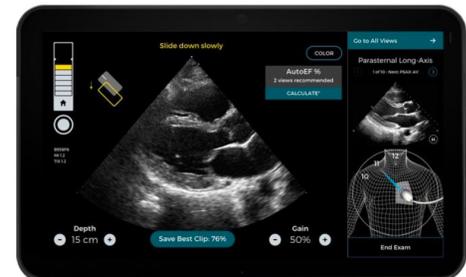
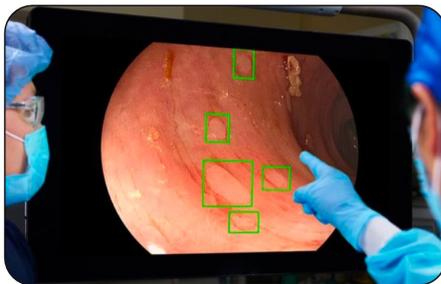# Ensuring Patient Access to Safe & Effective Digital Health Medical Devices
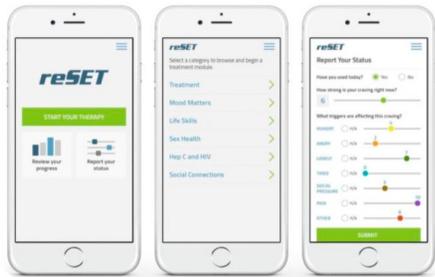
Providing Cognitive Behavioral Therapy for Substance Abuse Disorder (May 2016) Pear™
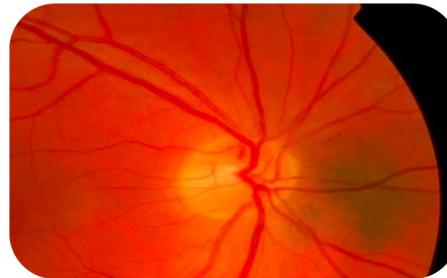
Detecting Retinopathy in Diabetic Patients (Apr 2018) IDx-DR™

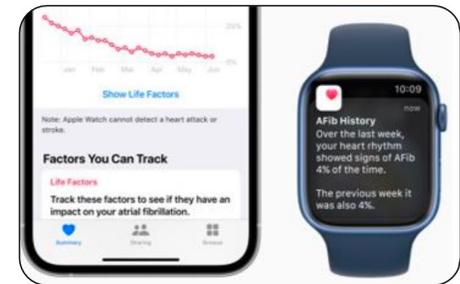Guiding Users in Obtaining Cardiac Ultrasound (Feb 2020) Caption Guidance™

Helping Detect Potential Signs of Colon Cancer (Apr 2021) GI Genius™

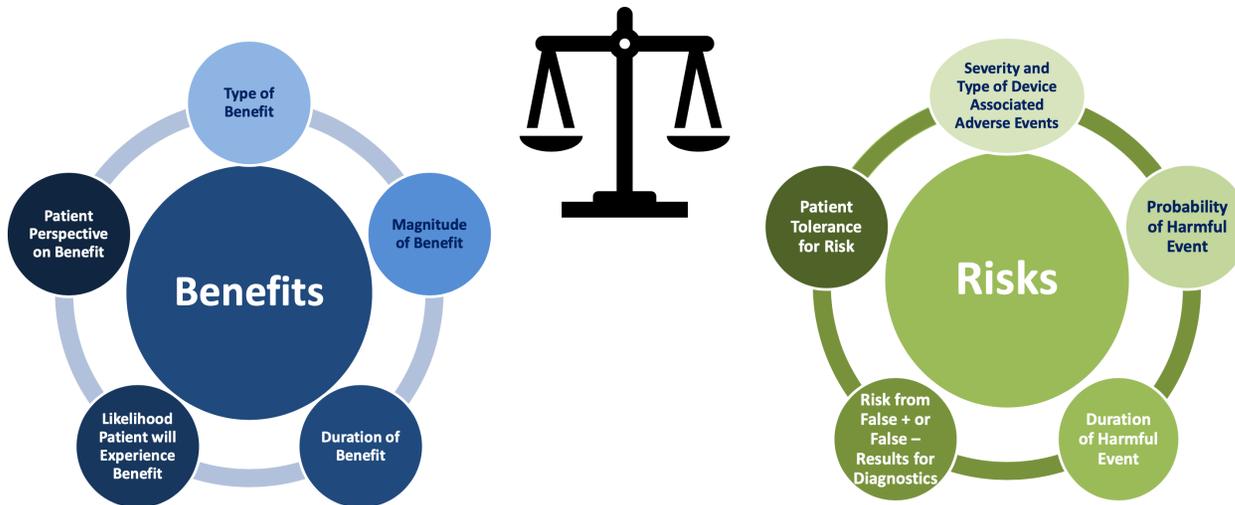Helping Identify Prostate Cancer (Sep 2021) Paige Prostate™

Measuring Burden of Atrial Fibrillation in Patients with Afib (Jun 2022) Apple™

www.fda.gov/digitalhealth

Evidence-based Assessment of Risks and Benefits

www.fda.gov/digitalhealth

AI-Enabled Devices: CDRH Efforts to Date

1,250+ FDA authorized AI-enabled Medical Devices marketed in the United States are here today

2019	2020	2021	2022	2023	2024	2025
			List Updated	**List Updated**	**List Updated**	**List Updated**
• AI/ML-SaMD Discussion Paper • Joined Collaborative Community related to AI/ML	• Public Workshop on AI/ML in Radiological Imaging • Patient Engagement Advisory Committee Meeting on Patient Trust in AI/ML Devices	• Posted List of Authorized AI/ML Devices • AI/ML Medical Device Software Action Plan • Public Workshop on Transparency of AI/ML Devices • Guiding Principles for Good Machine Learning Practice for Medical Device Development	• Contributed to IMDRF's Key Terms & Definitions: Machine Learning Enabled Medical Devices • Clinical Decision Support (CDS) Final Guidance • Recognized Consensus Standard on AI/ML	• Predetermined Change Control Plan for AI/ML Devices Draft Guidance • Formed Digital Health Advisory Committee • PCCP Guiding Principles	• AI & Medical Products paper on how CBER, CDER, CDRH, and OCP are working together • Centralized AI and Medical Products resources across FDA.gov • NPJ article on Transparency in AI/ML-enabled devices • With MHRA & HC ML Transparency Principles Document • First Digital Health Advisory Committee meeting (GenAI)	• PCCP for AI-enabled devices final guidance • Lifecycle of AI-enabled devices draft guidance • Co-led development of IMDRF Good ML Principles Document • Request for Public Comment: Measuring and Evaluating Performance of AI-enabled Medical Devices in the Real-World

Acronyms
Artificial Intelligence (AI)
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Clinical Decision Support (CDS)
International Medical Device Regulator Forum (IMDRF)
Health Canada (HC)
Machine Learning (ML)
Medicines and Healthcare products Regulatory Agency (MHRA)
Office of Combination Products (OCP)
Predetermined Change Control Plans for Medical Devices (PCCP)

21st Century Cures Act – Software Functions Excluded from Device Definition

WHAT IS IN:

*A Device is defined by the Federal Food, Drug, & Cosmetic Act, Section 201(h) 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:

- 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...

WHAT IS OUT:

These software functions were excluded from the "device" definition by the 21st Century Cures Act:

Administrative support of a health care facility;	Maintaining or encouraging a healthy lifestyle with no reference to any disease or condition;	Electronic patient record functions;	Transferring, storing, converting formats, or displaying data and results;	Some clinical decision support.
520(o)(1)(A)	520(o)(1)(B)	520(o)(1)(C)	520(o)(1)(D)	520(o)(1)(E)

Revised Guidance

The Cures Act excludes certain software functions from device definition if all four of these Criteria are met:

1) NOT intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system;

2) intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);

3) intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and

4) intended for the purpose of enabling a health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Clinical Decision Support Software

Guidance for Industry and Food and Drug Administration Staff

Document issued on January 29, 2026.

This document supersedes "Clinical Decision Support Software" issued on January 6, 2026.

For questions about this document regarding CDRH-regulated devices, contact the Digital Health Center of Excellence via email at DigitalHealth@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at industry.biologics@fda.hhs.gov. For questions about this document regarding CDER-regulated products, contact Center for Drug Evaluation and Research, Food and Drug Administration at druginfo@fda.hhs.gov. For questions about this document regarding combination products, contact the Office of Combination Products at combination@fda.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Office of Combination Products in the Office of the Commissioner

Thank you

✉ **shantanu.nundy@fda.hhs.gov**