Statistical Considerations for Precision Medicine in Psychiatry and Neurology: A Regulatory Perspective

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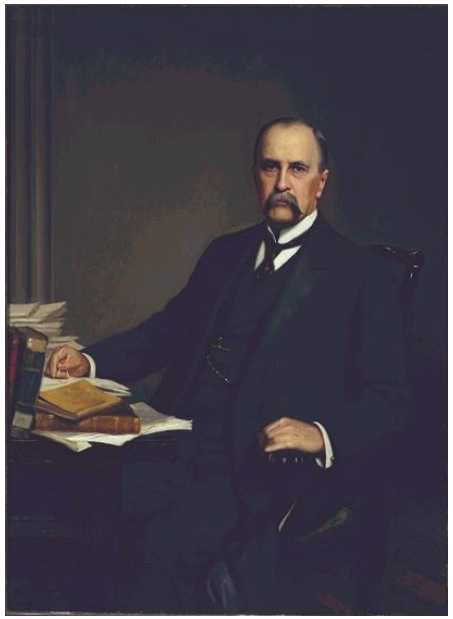
Disclaimer

* This presentation reflects the view of the author and should not be construed to represent the FDA's views or policies.

The Problem of Variability



Sir William Osler

(1849-1919)

"Variability is the law of life, and
as no two faces are the same,
so no two bodies are alike,
and no two individuals react alike,
and behave alike under the abnormal
conditions, which we know as disease."

As Science and Biotechnologies Evolve

- Watson & Crick discovered the structure of DNA in 1953: 50th anniversary at NIH in 2003
- FDA Inter-center Pharmacogenomics Committee initiated 2002, led to voluntary (exploratory) genomic data submission, machine learning techniques had been actively utilized in research
- Personalized Medicine session, FDA Centennial Science Forum Celebration, DC, Oct. 2006
- Pharmacogenomics/pharmacogenetics (Gene Expression, GWS, NGS)
  - Definitions, genomic data, sample coding categories
- Biomarker as drug development tools for qualification at FDA began in 2007
  - Context, Structure, Format of Qualification submission
- Targeted Drug development: Guidance on In Vitro Companion Diagnostic Devices (2014), Guidance on Clinical Trial Enrichment Strategies (2019)
- FDA Biomarker Working Group on Multicomponent Biomarker (2023)*
- Methodologies include Artificial Intelligence, Machine Learning, Deep Learning, …..
- Main interests: efficacy and safety of an investigational drug in drug development

*Agyeman AS, Bandukwala A, Bouri K, Hawes J, Krainak DM, Lababidi S, Mattes WB, Mishina EV, Turfle P, Wang SJ, Thekkudan T, on behalf of the US FDA Biomarker Working Group. (2023). US FDA public meeting: identification of concepts and terminology for multicomponent biomarkers. Biomarkers in Medicine 17(11):523-531.

Pathway to Personalized Medicine:

Getting the best treatment to the individual

A Multidisciplinary Approach is Needed:

- Molecular Scientists
- Biotechnology, e.g., Omics
- Imaging standards
- Bioinformatics
- Statistical Classification Algorithms
- Medical researchers

Personalized Medicine 2006

FDA NEWS

THE FOOD AND DRUG ADMINISTRATION / AN AGENCY OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
P05-53
August 22, 2005

Media Inquiries: **Julie Zawisza**
301-827-6242
Consumer Inquiries: **888-INFO-FDA**

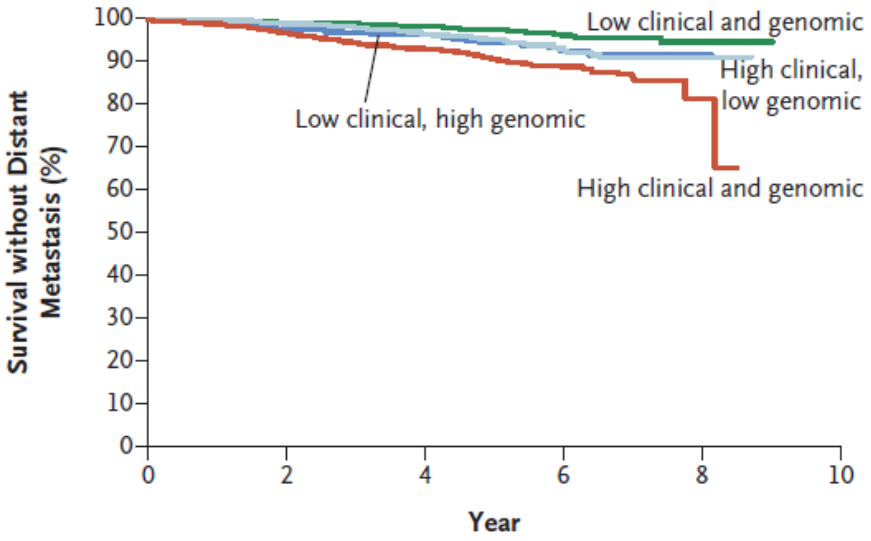
FDA CLEARS GENETIC TEST THAT ADVANCES PERSONALIZED MEDICINE
Test Helps Determine Safety of Drug Therapy

Today, FDA cleared for marketing a new blood test that will help doctors make personalized drug treatment decisions for some patients. The Invader UGT1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. Doctors can use this information to help determine the right drug dosage for individual patients, and minimize harmful drug reactions.

"This test represents the power of DNA-based testing to provide individualized medical care," said Daniel Schultz, MD, Director of FDA's Center for Devices and Radiological Health. "These technologies can significantly improve patient management and reduce the risk of ineffective or even harmful drug therapy by telling doctors how to individualize drug dosing."

An early example: Agendia MammaPrint

- The 70-gene signature was developed by supervised microarray analysis, applied machine learning algorithm, using stored tissue and data collected from women who are at risk for distant metastasis but were not treated with systemic therapy
- The first FDA cleared in vitro diagnostic multivariate index assay (IVDMIA) device in 2007
  - *The MammaPrint® result is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors.*
  - *MammaPrint® is not intended for diagnosis, or to predict or detect response to therapy, or to help select the optimal therapy for patients.*
- Used as prognostic factor in clinical trials, e.g., MINDACT trial, to assess the effectiveness of an experimental treatment.



No. at Risk					
Low clinical and genomic risk	2745	2628	2331	735	33
Low clinical, high genomic risk	592	550	484	136	2
High clinical, low genomic risk	1550	1457	1317	311	9
High clinical and genomic risk	1806	1689	1462	395	11

Figure 3. Survival without Distant Metastasis in the Four Risk Groups.

The analysis includes all enrolled patients, and the risk groups are based on corrected risk. The time-to-event curves were estimated by means of the Kaplan–Meier method.

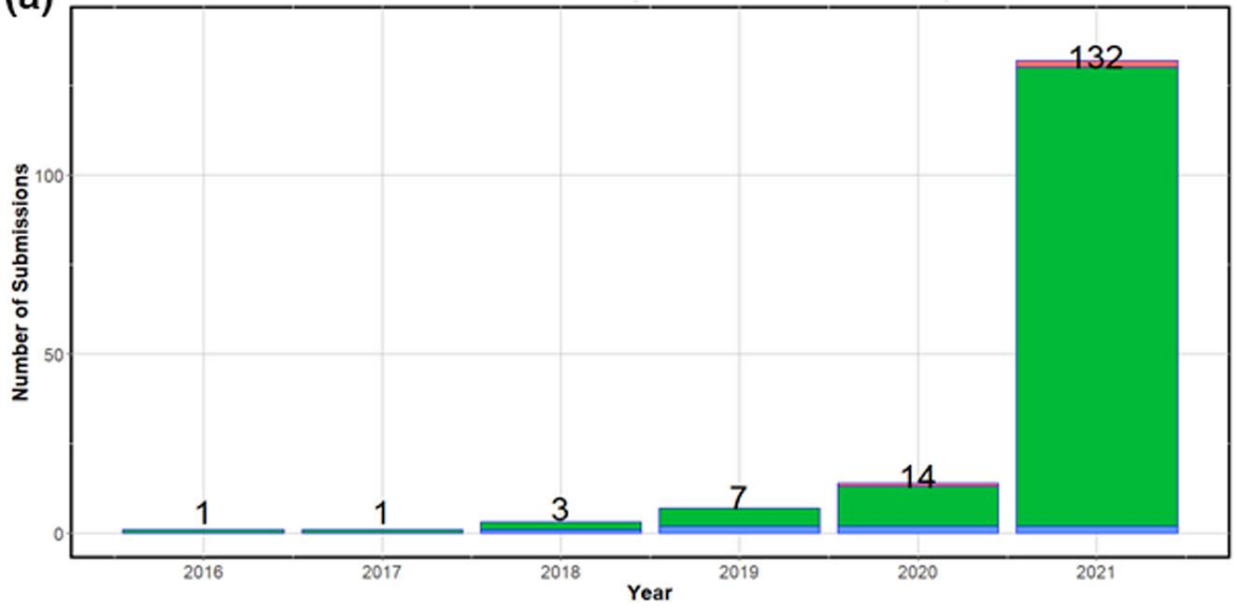
Artificial Intelligence

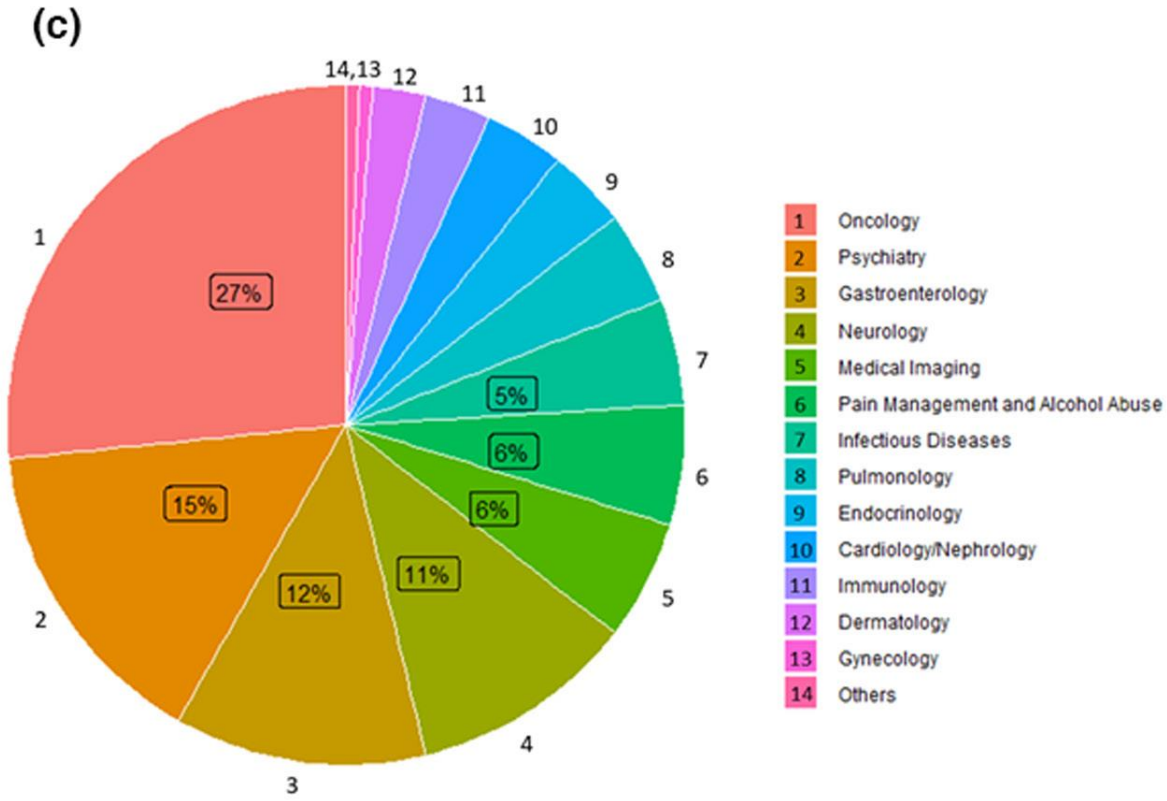
EO 14110 (executive order on the safe, secure, and trustworthy development and use of artificial intelligence)

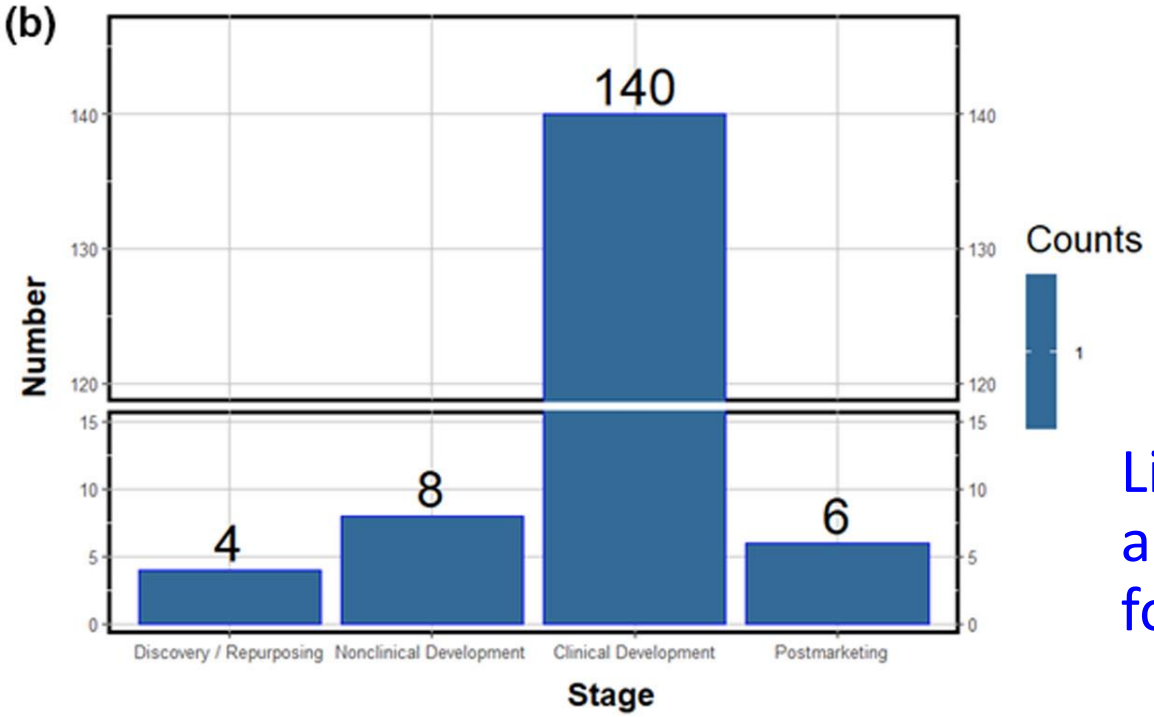
The term “artificial intelligence” or “AI” has the meaning set forth in 15 U.S.C. 9401(3): a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations, or decisions influencing real or virtual environments. Artificial intelligence systems *use machine- and human-based **inputs** to perceive real and virtual environments*; abstract such perceptions into models through analysis in an automated manner; and use **model inference** to formulate options for information or action.

WH.gov, October 30, 2023

For drug developments, application of AI/ML are mostly seen in INDs during clinical developments; CNS related (15%+11%+6%=32%)

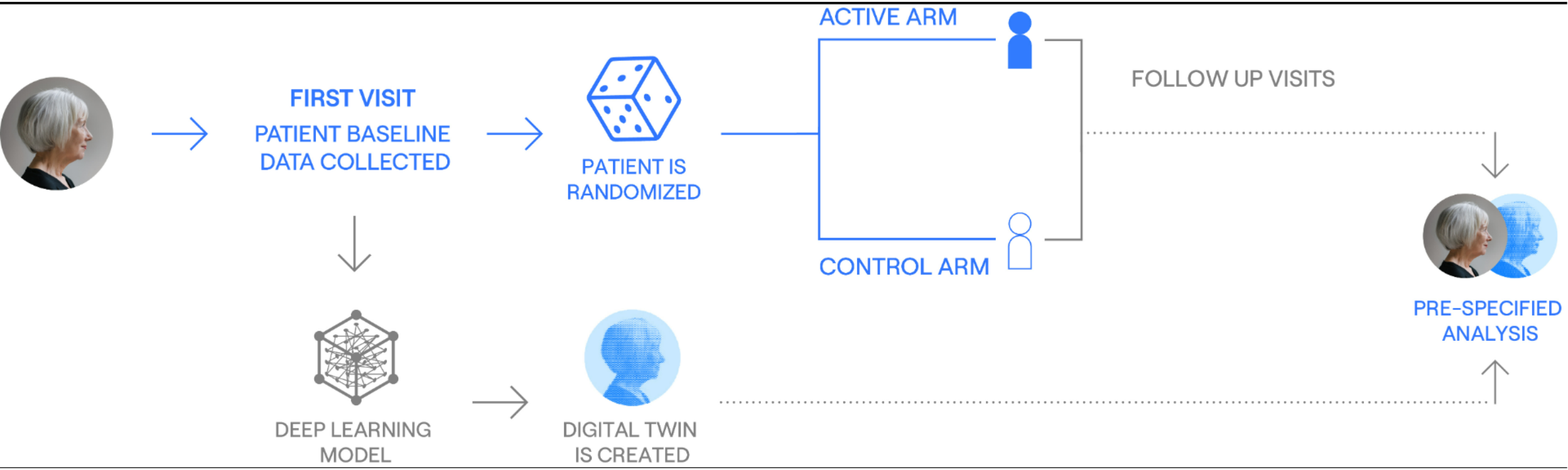






Liu et al. (2023) Landscape analysis of the application of AI and ML in regulatory submissions for drug development 2016-2021

A recent example: Unlearn AI PROCOCA*



A statistical methodology for incorporating prognostic scores derived from trial participants' digital twins into the design and analysis of phase 2 and phase 3, initially chose Alzheimer's Disease

*https://www.statnews.com/sponsor/2022/11/09/rcts-with-prognostic-digital-twins-overcome-the-limitations-of-external-control-arms/

US FDA Comments*

1.We appreciate your interest in statistical methodology intended to improve the efficiency of clinical trials by using trial subjects' predicted outcomes on placebo (prognostic scores) in covariate adjustment with linear models in order to increase the precision of treatment effect estimation and statistical power.

2.Based on our review of your LOI, PROCOVA is in principle a special case of an Analysis of Covariance (ANCOVA). This type of model is expected to improve the precision of statistical analysis in clinical trials.

3.If a prognostic covariate is derived using independent external data, then it is valid to adjust for this pre-specified covariate in an ANCOVA in a prospective trial. PROCOVA may or may not lead to a more precise treatment effect estimate than more traditional ANCOVA modeling. This likely will depend on the prognostic value of the PROCOVA covariate in its intended study population.

4.A power calculation may be optimistic if the correlation between a derived covariate and an outcome of interest differs between external data and the prospective trial in which the covariate will be used for adjustment. An unadjusted sample size calculation will often be conservative and help prevent underpowered trials. This is usually a good practice, and conservatism is often warranted in sample size planning.

5.While preparing the guidance "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products," we worked with comments from the public docket. We concur with EMA that PROCOVA is a special case of ANCOVA. As such, CDER's current feedback is that PROCOVA does not appear to deviate from our guidance. Any future requests related to its use should be product or trial specific and directed by a sponsor to the appropriate review division.*

*US FDA comments on Unlearn's PROCOVA methodology (linkedin.com) (Jan. 02, 2024)
*https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products

FDA's ISTAND Pilot Program accepts submission of first artificial intelligence-based and digital health technology for neuroscience

[1/23/2024] FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) recently accepted a new submission into the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program (https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program). This submission is the first artificial intelligence-based and digital health technology-based project and the first project in neuroscience to be accepted into ISTAND.

"This marks a pioneering step for the ISTAND program as the first artificial intelligence-based, digital health technology project in neuroscience to be accepted into the pilot program," said Peter Stein, M.D., director of CDER's Office of New Drugs. "Our acceptance aligns with FDA's vision of optimizing drug development and evaluation, potentially expediting the availability of safe and effective treatments."

Launched in 2020, ISTAND aims to support the development of novel drug development tools (DDTs) to be used in regulatory applications for new medical products. The program opens opportunities for DDTs that do not fit into established pathways for evaluation and application such as for biomarkers and clinical outcome assessments.

An automated depression and anxiety severity measurement tool utilizing multiple behavioral and physiological indices of depression in a machine learning (ML) model to derive clinician-reported outcomes for depression and anxiety based on the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) scores. This LOI represents both a digital health technology (DHT) and artificial intelligence (AI)/ML, both important areas of focus for FDA.

https://www.fda.gov/drugs/drug-safety-and-availability/fdas-istand-pilot-program-accepts-submission-first-artificial-intelligence-based-and-digital-health

Most uptake appears to be in clinical R&D during IND investigation

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Challenges with AI/ML for drug development

- Data quantity and quality
  - High quality, large scale and fit for purpose datasets are needed
- Integrating domain knowledge into AI models (input step)
- Accounting for longitudinal dependences in data
- Important to leverage data from multiple institutions
- Data privacy and security, and ethical use of datasets
- Transparency vs black box
- Development through training/validation represent preliminary performance
- If reliance on RWD is critical, high quality RWD is key to success of AI model output and interpretability

Interim Remarks

- AI/ML is increasingly being applied in drug R&D, safety evaluation, large language model, etc. and innovations continue
- Main interests are efficacy and safety of investigational drugs or repurposing
- Acknowledgement of practical challenges for precision medicine
- To foster Innovative Science and Technology Approaches for New Drugs (ISTAND), FDA's CDER's recent acceptance of a new submission in neuroscience into the ISTAND program: "… marks a pioneering step … Our acceptance aligns with FDA's vision of optimizing drug development and evaluation, potentially expediting the availability of safe and effective treatments." said Peter Stein, MD, Director of CDER' Office of New Drugs

Thank you