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RESEARCH COMPLIANCE AND INTEGRITY

Research Compliance and Integrity Hot Topics Session

Artificial Intelligence and Human Subjects Research
Office of IRB Administration (OIA)

January 29, 2025

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Artificial Intelligence & Human Subjects Research

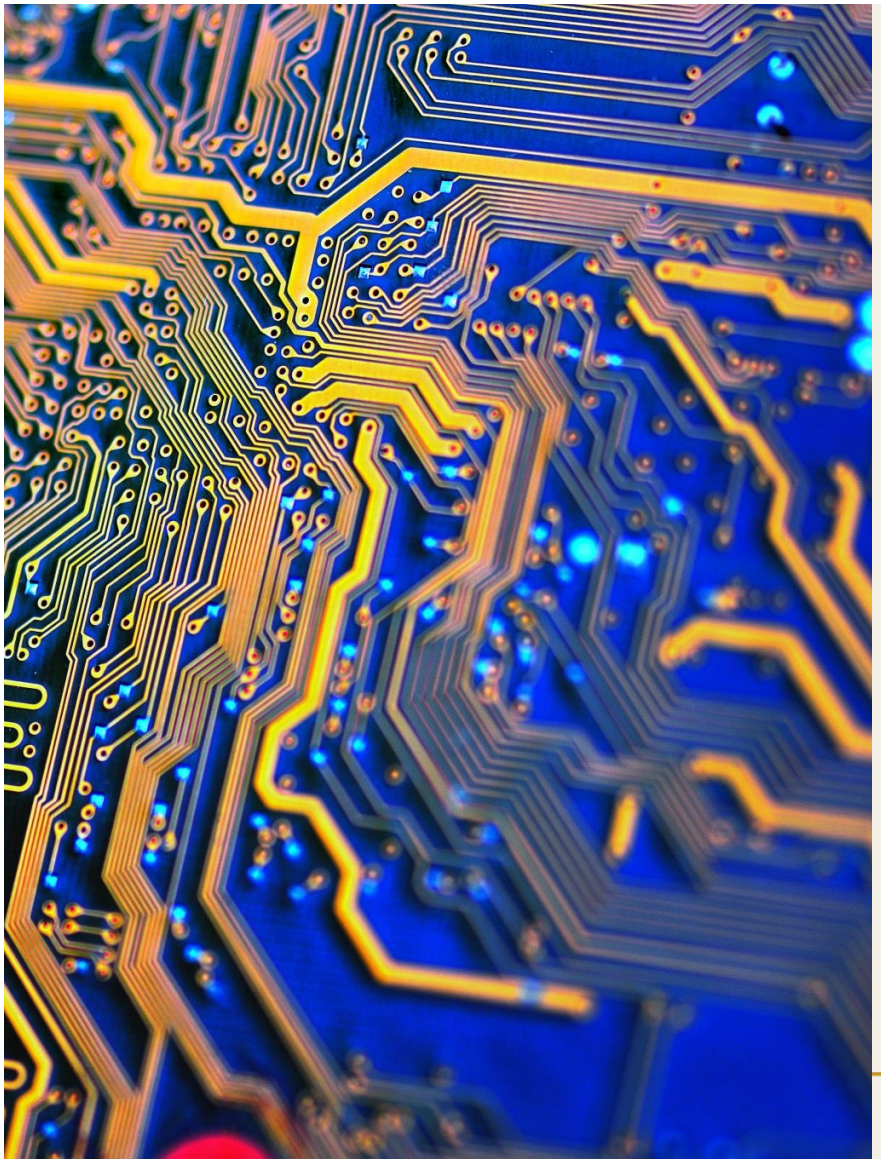
Kacey RF Pratt, Interim Director, Office of IRB Administration | January 29, 2025

Outline

- What is Artificial Intelligence?
- What is Human Subjects Research?
- Reviewing AI research under the Common Rule
  - Is it Human Subjects Research?
  - Is it Exempt?
  - Can it be reviewed Expedited?
  - Does it need to be reviewed by the Full Board?
- Reviewing AI research under the FDA regulations
  - Medical Devices and Software as a Medical Device (SaMD)
  - Clinical Decision Support (CDS)
- Q & A

What is Artificial Intelligence?

- A few different definitions:
  - From *Artificial Intelligence: A Modern Approach* - "It is a field of research in computer science that develops and studies methods and software that enable machines to perceive their environment and use learning and intelligence to take actions that maximize their chances of achieving defined goals."
  - From Google – "Artificial intelligence (AI) is a set of technologies that enable computers to perform a variety of advanced functions, including the ability to see, understand and translate spoken and written language, analyze data, make recommendations, and more."
  - From Encyclopedia Britannica – "the ability of a digital computer or computer-controlled robot to perform tasks commonly associated with intelligent beings."



AI is…

- …a machine's ability to "think" like a human.
- …a field of science concerned with building "smart" computers
- …a broad field professionally
- …for business use, AI is a set of technologies used for a broad array of functions

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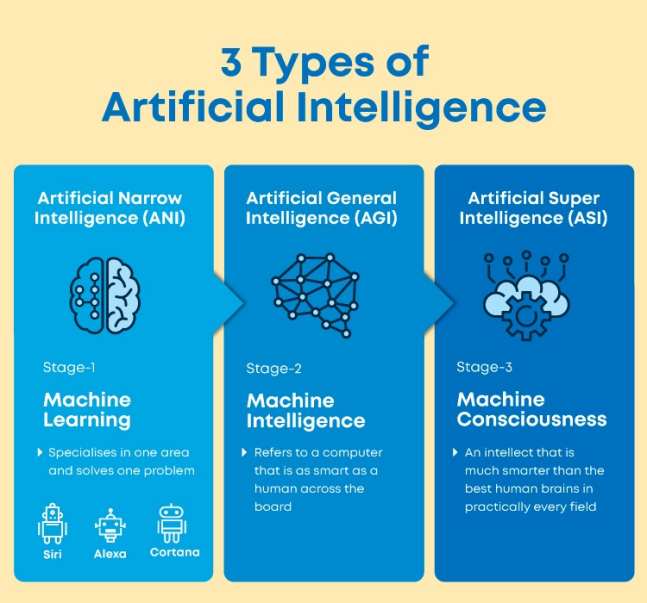
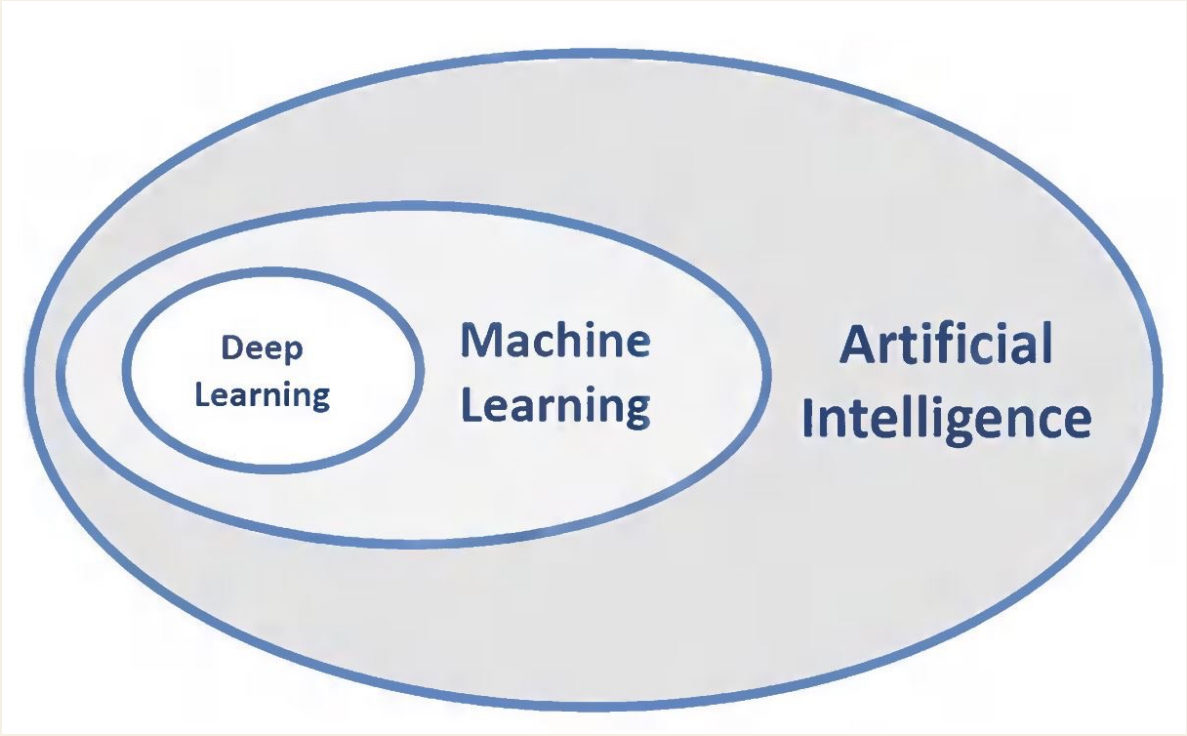
“What can the machine do?”




Deep
Learning
Machine
Learning
Artificial
Intelligence

Machine Learning

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History Time

Terms that also refer to AI:

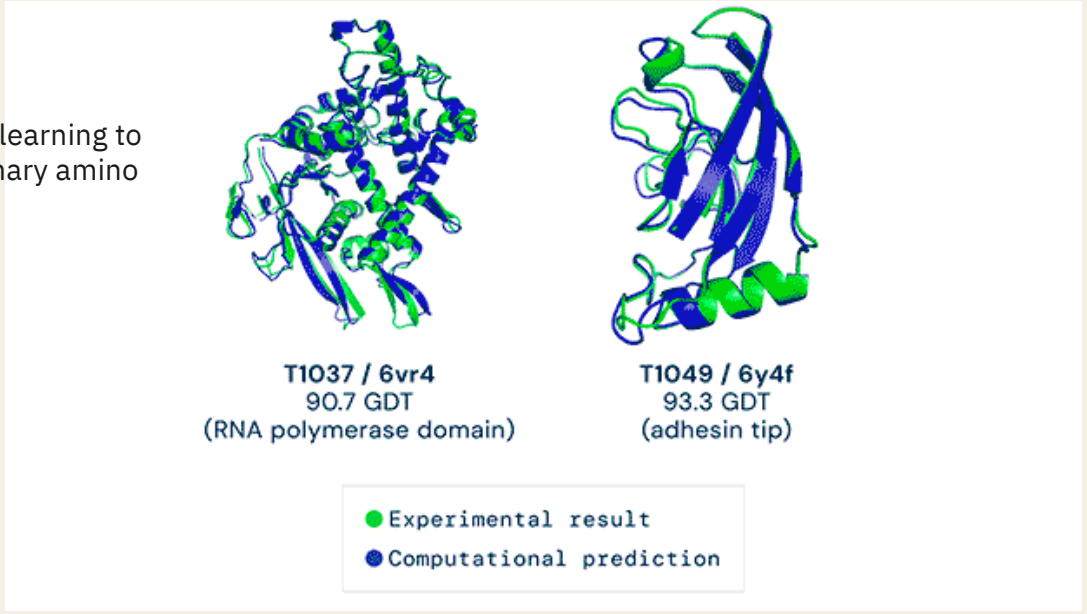
- Algorithm
- Model
- Machine Learning
- Deep Learning
- Neural Networks
- Large Language Model (LLM)

Examples of AI in Use Today

- Facebook Friends Recommendations
- Siri, Alexa and other smart assistants
- Self-driving cars
- Robo-advisors
- Conversational bots
- Email spam filters
- Netflix recommendations
- Disease mapping
- Automated financial investing
- Virtual travel booking agent
- Social media monitoring
- Spotify DJ
- Grammarly
- Student/learner assistance (StudyMonkey, Duolingo)
- **Healthcare management**
- **Assisted Diagnosis (many examples in radiology)**
- **Robot-assisted surgery**
- https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

Predicting Protein Structure

- AlphaFold from Google DeepMind
- A multicomponent AI system that uses machine learning to predict a protein's 3D structure based on its primary amino acid sequence.



What is Human Subjects Research?

The Common Rule Definition (45 CFR 46.102(e)&(l))

- Research – a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.
- Human Subject – a living individual about whom an investigator (whether professional or student) conducting research:
  - Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
  - Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

What is Human Subjects Research?

The FDA General Definition (21 CFR 56.102(c)&(e))

- Clinical Investigation – any experiment that involves a test article and one or more human subjects…
- Human Subject – an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

The FDA Drug/Biologic Definition (21 CFR 312.3(b))

- Subject – a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

The FDA Device Definition (21 CFR 812.3(p))

- Subject – a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

Reviewing AI Research Under the Common Rule

First:

- Is it research?
  - Is it a systematic investigation?
    - Often “Yes”
  - Is it designed to develop or contribute to generalizable knowledge?
    - Often more tricky to answer
- Example:
  - Designing and developing a chat bot to help me learn French.
    - Probably systematic, not generalizable if it will only work for me.
  - Designing and developing a chat bot that helps anyone learn French.
    - Probably systematic, generalizable since it applies to a broad population.

Reviewing AI Research Under the Common Rule

If it is research, next we ask:

- Does it involve human subjects?
  - Does it involve information **about** or biospecimens from a living individual?;
  - Does it involve the use, study, or analysis of the information or biospecimens?;
  - AND:
    - Are the information or biospecimens collected through intervention, interaction with the individual? OR
    - Are the information or biospecimens obtained or generated by the researchers **AND** is the information private and identifiable or are the biospecimens identifiable?

Reviewing AI Research Under the Common Rule

- Examples:
  - An anonymous survey of students on their political opinions
    - It's **about** the individuals and collected through an interaction (the survey)
  - A survey of farm workers to understand the farm's policies on antibiotic use
    - It's an interaction (the survey) but is it **about** the farm operations or the individuals?
  - Putting scents in classrooms on exam day to see how students do
    - It's **about** the individuals (test scores), involves an intervention (the scent), and uses private information (student data). May or may not be identifiable depending on source.
  - Doing a chart review of patients to see why some stay in hospital longer
    - It's **about** the individuals, no interaction or intervention, requires obtaining identifiable private information (the medical record)
  - Using a de-identified dataset to train an algorithm to detect bias
    - It's **about** the individuals, no interaction, no intervention, no biospecimens, no identifiable private information

Reviewing AI Research Under the Common Rule

- If it is human subjects research, is it Exempt?
  - Exempt research is a type of human subjects research
  - Does not require full IRB considerations under the Common Rule
- Must fit into one or more of 8 federal categories
  - Cat 1: Normal educational practices
  - Cat 2: Surveys, interviews, educational tests, observation of public behavior
  - Cat 3: Benign behavioral interventions
  - Cat 4: Secondary research where consent is not required
  - Cat 5: Government research
  - Cat 6: Food quality and taste evaluation
  - Cat 7: Storage of data and biospecimens for secondary research with broad consent
  - Cat 8: Secondary research using broad consent

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  - Cat [illegible] Storage of data and biospecimens for secondary research with broad consent
  - Cat [illegible] Secondary research using broad consent

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Reviewing AI Research Under the Common Rule

- Exempt Examples:
  - Interviews of adults to train an AI to speak like a human
    - Research, Involves Human Subjects (interaction), Meets Exempt Cat 2
  - AI review of student records to find trends in learning styles
    - Research, Involves Human Subjects (identifiable private information), Meets Exempt Cat 4
    - Note: FERPA considerations would apply. Check with the registrar.
  - Adults interacting with an AI and a researcher to see if they can “guess the human” to understand what traits “give away” the machine
    - Research, Involves Human Subjects (interaction and intervention), Meets Exempt Cat 3

Reviewing AI Research Under the Common Rule

- It's research, has human subjects, it's not exempt. What now?
- Can it be Expedited?
  - Must be minimal risk;
  - Must not place participants at risk of criminal or civil liability, be damaging to financial standing, employability, insurability, reputation, or be stigmatizing **unless** there are reasonable and appropriate protections in place; **and**
  - Must fit into one or more of 7 federal categories:
    - Cat 1: FDA clinical investigations not requiring an IND or IDE
    - Cat 2: Blood draws up to certain limits
    - Cat 3: Non-invasive collection of specimens
    - Cat 4: Non-invasive collection of data
    - Cat 5: Secondary data uses
    - Cat 6: Data collection from voice, video, digital, or image recordings
    - Cat 7: Research on characteristics/behavior or using surveys, interviews, oral history, etc.

Reviewing AI Research Under the Common Rule

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  - Must fit into one or more of 9 federal categories:
    - Cat 1: FDA clinical investigations not requiring an IND or IDE
    - Cat 2: Blood draws up to certain limits
    - Cat 3: Non-invasive collection of specimens
    - Cat 4: Non-invasive collection of data
    - Cat 5: Secondary data uses
    - Cat 6: Data collection from voice, video, digital, or image recordings
    - Cat 7: Research on characteristics/behavior or using surveys, interviews, oral history, etc.

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Reviewing AI Research Under the Common Rule

- Expedited Examples:
  - Studying how AI when integrated into EMR can improve responses to MyChart messages
    - Research, Human Subjects (identifiable private information), not exempt, Expedited 5
  - Studying AI production of different dialects using participant speech recordings made for research purposes
    - Research, Human Subjects (interaction), not exempt, Expedited 6
  - Collecting oral histories from participants to train AI algorithms on storytelling
    - Research, Human Subjects (interaction), not exempt, Expedited 7

Reviewing AI Research Under the Common Rule

- It’s research
- It involves human subjects
- It’s not Exempt
- It’s not Expedited
- Now what?

Reviewing AI Research Under the Common Rule

- It’s research
- It involves human subjects
- It’s not Exempt
- It’s not Expedited
- Now what?

- Full Board review!

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Reviewing AI Research Under the Common Rule

- Full Board Examples:
  - Blindfolding a participant and seeing how well AI can guide them through busy city streets
  - Assigning prisoner housing arrangements based on AI review of their records and seeing how this affects their recidivism
  - Assigning academic counseling resources to students based on AI determination and assessing for desired scholastic success

FDA Regulated AI

When do FDA regulations apply?

What are we doing here at UCSD or at relying sites using UCSD IRB as IRB of record?

- When we are selected as a clinical site for the study
- When the researchers are “clinical investigators”
  - An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article (AI) is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.
  - Usually, secondary use studies where UCSD data is shared with an external AI developer (commercial or non-profit), and model is housed externally, the local activities are not considered FDA-regulated
    - Local requirements may change as regulatory guidance is issued and institutional concerns identified (e.g., HDOC)

FDA-regulated AI

- Annual continuing review always required
- No exempt categories of IRB review analogous to Common Rule
- Expedited categories are the same as Common Rule
  - Cat 1: FDA clinical investigations not requiring an IND or IDE
  - Cat 2: Blood draws up to certain limits
  - Cat 3: Non-invasive collection of specimens
  - Cat 4: Non-invasive collection of data
  - Cat 5: Secondary data uses
  - Cat 6: Data collection from voice, video, digital, or image recordings
  - Cat 7: Research on characteristics/behavior or using surveys, interviews, oral history, etc.

FDA-regulated AI

- Could be reviewed under category 1 if:
  - AI is a medical device whose safety and/or efficacy is the object of the study AND
  - It is to be used in the study in accordance with its FDA-approved indication OR
  - It is a diagnostic that will be validated by the ”gold standard”
- Potentially categories 5, 7 if it is not the object of the study (e.g., it is being used to collect or create a measurement or other factor that the study will use in the analysis of its data to test the study hypothesis)

Medical Device – § 201(h)(1) FD&C Act

- instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
- (A) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- (B) 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
- (C) 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 …and which is not dependent upon being metabolized...

Object of Study

- Studying safety (characterize adverse effects & their frequency)
- Studying efficacy (effectiveness – does it work?)

AI Research regulated by FDA
21 CFR 812 – Device Investigations

- Medical device – yes
- Object of study - yes

Is the AI/software investigational as used in the study?

- Being used in accordance with its approved indication
  - NO, use is not investigational but is still object of the study (if minimal risk, could possibly be expedited category 1)
- Has FDA approval/510(k) clearance & but being used off-label
  - YES, investigational
- Has no FDA approval
  - YES, investigational

Clinical Decision Support Tools: FDA Enforcement Discretion

- Excluded from enforcement of 812 if the software functions meet **all** of the following four criteria:
  - (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
  - (4) intended for the purpose of enabling such ***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

So where are we?

- FDA regulations apply to our activities
- AI meets definition of medical device
- AI is object of the study
- AI does not have FDA approval/510(k) clearance for use in the study
- AI does not meet criteria for enforcement discretion

- What do we do next???

Review by the Full Board

- Convened IRB will make a “device determination” as to the risk of the device
  - Non-significant Risk
  - Significant Risk
- FDA is final arbiter of NSR v. SR
- If the AI already has an IDE issued by FDA, IRB will not assess NSR v. SR because FDA already has
  - Most commonly occurs when the study is sponsored & authored by industry

Significant Risk Device

- an investigational device that:
  - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- Requires submission to FDA for an IDE – gets a “number”
- Investigator requirements (obligations to FDA/sponsor) per 21 CFR 812
  - Appendix B-2 of IRB Handbook

Non-Significant Risk device

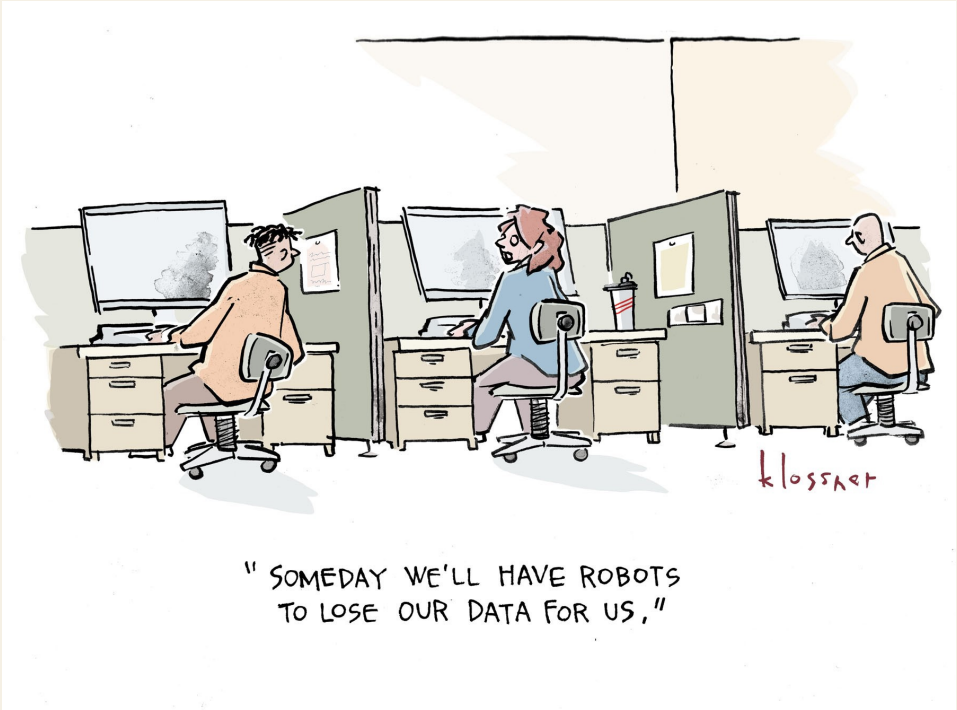
- “An NSR device study is one that does not meet the definition for an SR device study."
- IRB is empowered to make this determination as proxy for FDA
- NSR determination is considered an “approved IDE”
- Abbreviated requirements (obligations to FDA) per 21 CFR 812
  - IRB Handbook Appendix B-2

Informed Consent & HIPAA authorization

- Exempt – consent not required when no interaction/intervention with subjects from whom the data is coming. Eligible for HIPAA waiver if HIPAA applies.
- Expedited
  - Secondary use data generally qualifies for a waiver of consent & HIPAA authorization, but may not in all circumstances
- Full board
  - When device is NSR and study overall is found to be minimal risk, with no other procedures requiring written consent, study will often qualify for waivers of consent & HIPAA
  - SR device study will require written consent

What are we seeing in OIA?

- NHSR & exempt secondary data sharing
- The majority of investigational AI that comes before the convened IRB is determined to be NSR
  - This may not always be the case as model development continues toward greater use in medical decision making for patients
- Continuing to evolve:
  - Regulatory framework, requirements, & guidance
  - Understanding of risk
  - IRB approach
  - Institutional requirements



QUESTIONS & DISCUSSION

COMMUNICATIONS

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- Conflict of Interest Helpline: (858) 534-6465, info-coi@ucsd.edu
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