HRPP Clubhouse
Monday, October 1, 2024

A STREAMLINED & COMPLIANT IRB REVIEW OF ARTIFICIAL INTELLIGENCE in HUMAN SUBJECTS RESEARCH (AI HSR) (BIOMEDICAL VERSION)

Presenter:
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Director, Research Operations
Mayo Clinic
Human Research Protection Program (HRPP) &
Institutional Review Board (IRB)

“Scientific evidence is the language of **trust** in healthcare.”

Gretchen Purcell-Jackson, MD, PhD

AMIA Past-President and Board Chair

§ 46.111 Criteria for IRB Approval of Research

*"**In order to approve research**…the IRB shall determine that…Risks to subjects are minimized…By using procedures that are **consistent with sound research design** and that do not unnecessarily expose subjects to risk…"*

-45 CFR 46.111(a)(1)(i)

Ethical Principles for Medical Research Involving Human Subjects

*"Medical research involving human subjects must **conform to generally accepted scientific principles**, be based on a **thorough knowledge of the scientific literature**…The design and performance of each research study involving human subjects must be clearly described and justified..."*

-Declaration of Helsinki

(required under GCP and ICH E6(R2))

The Systematic Assessment of Risks and Benefits

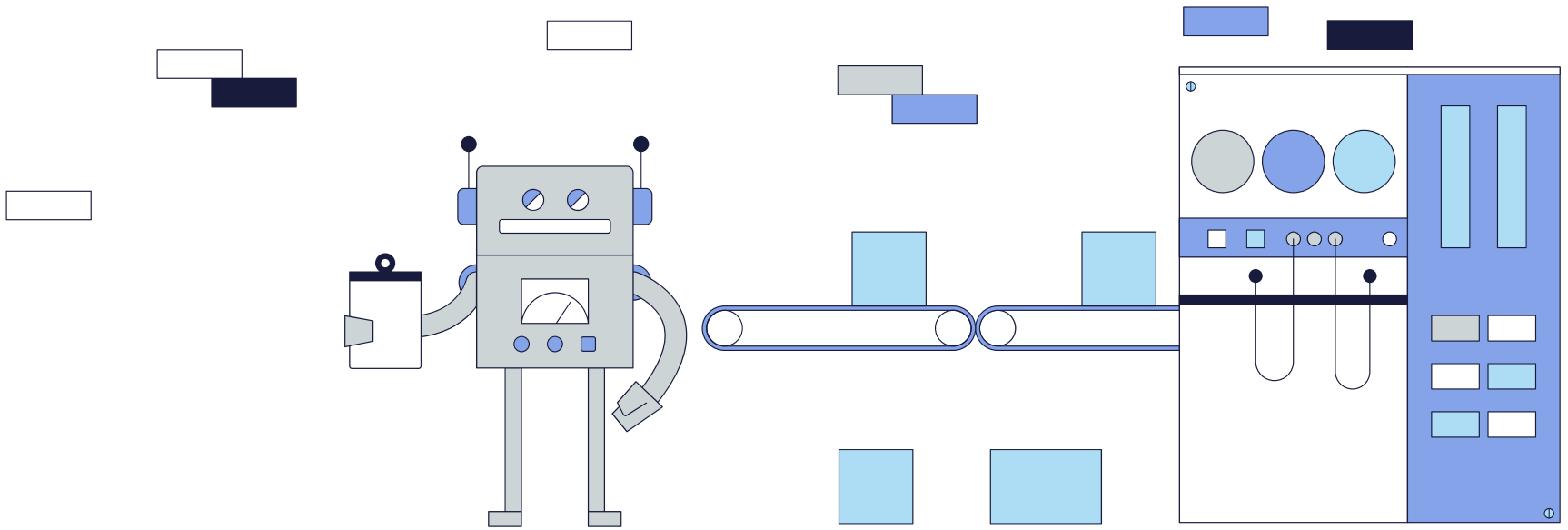
*"This ideal requires those making decisions about the justifiability of research to **be thorough in the accumulation and assessment of information about all aspects of the research**,…there should first be a **determination of the validity of the presuppositions of the research**; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible."*

-The Belmont Report

Learning Objectives

1. **Demystifying AI**
2. **A Long History of Regulating Software Functions**
3. **Simplifying AI IRB Review: A 3-Phased Approach**
4. **REGULATORY GREY AREAS**

   Recommendations for Navigation



Artificial Intelligence

*Machine-based system that, for **explicit** or **implicit** objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments.* [OECD]

EXPLICIT [knowledge based]:

- *Directly programmed in the system by a human developer*
- ***Example:** Early Expert AI systems*

*** Google translate**

*** Basic email spam filters**

*** Facial recognition**

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IMPLICIT [ML and Deep Learning]:

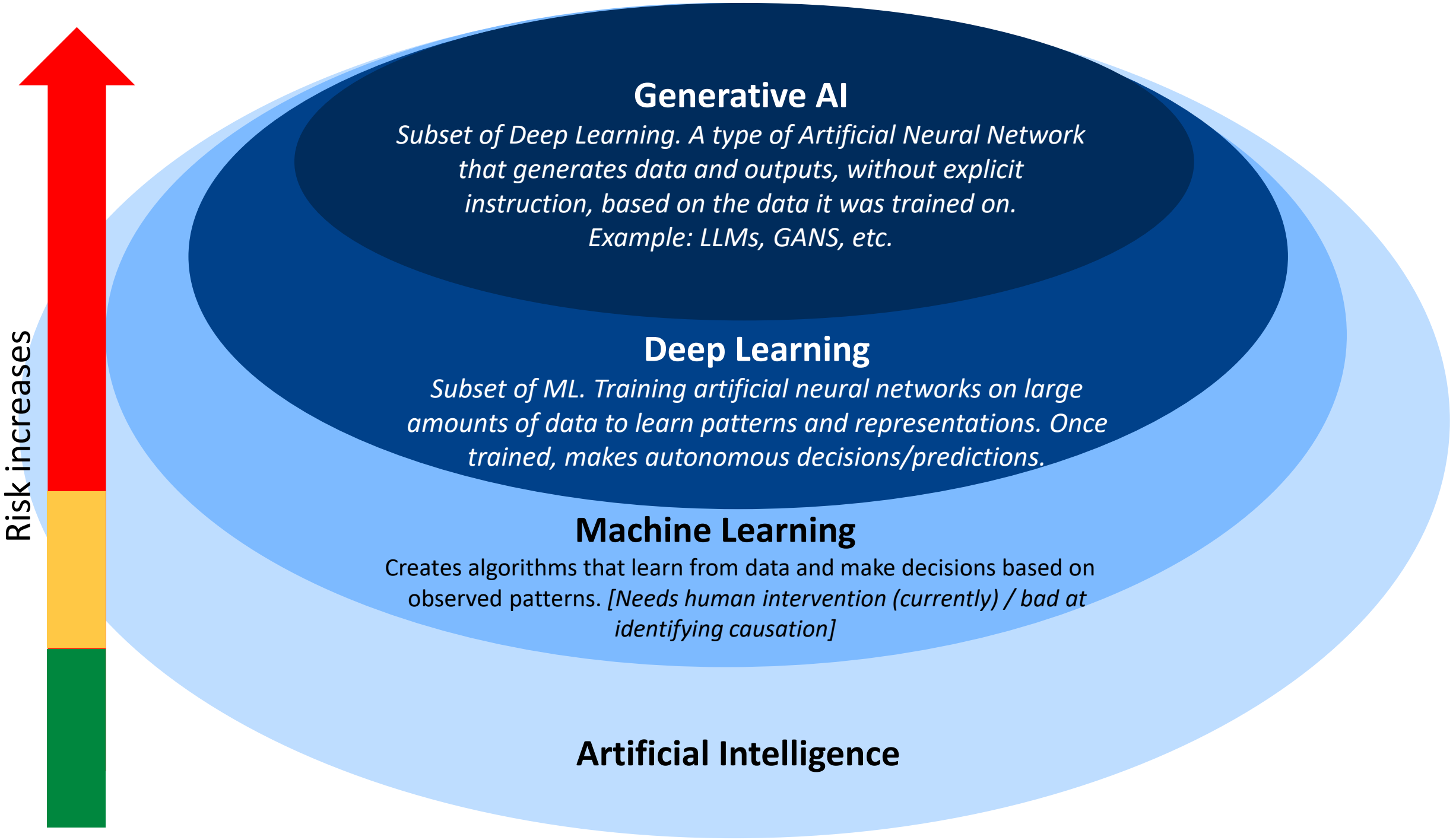
- *Creates algorithms that learn from data and make decisions based on observed patterns.*
- *Programmed by a set of rules specified by a human, BUT which programming may change when the system is capable of learning new objectives.*

*** Social media filters, Netflix recommendations, etc.**

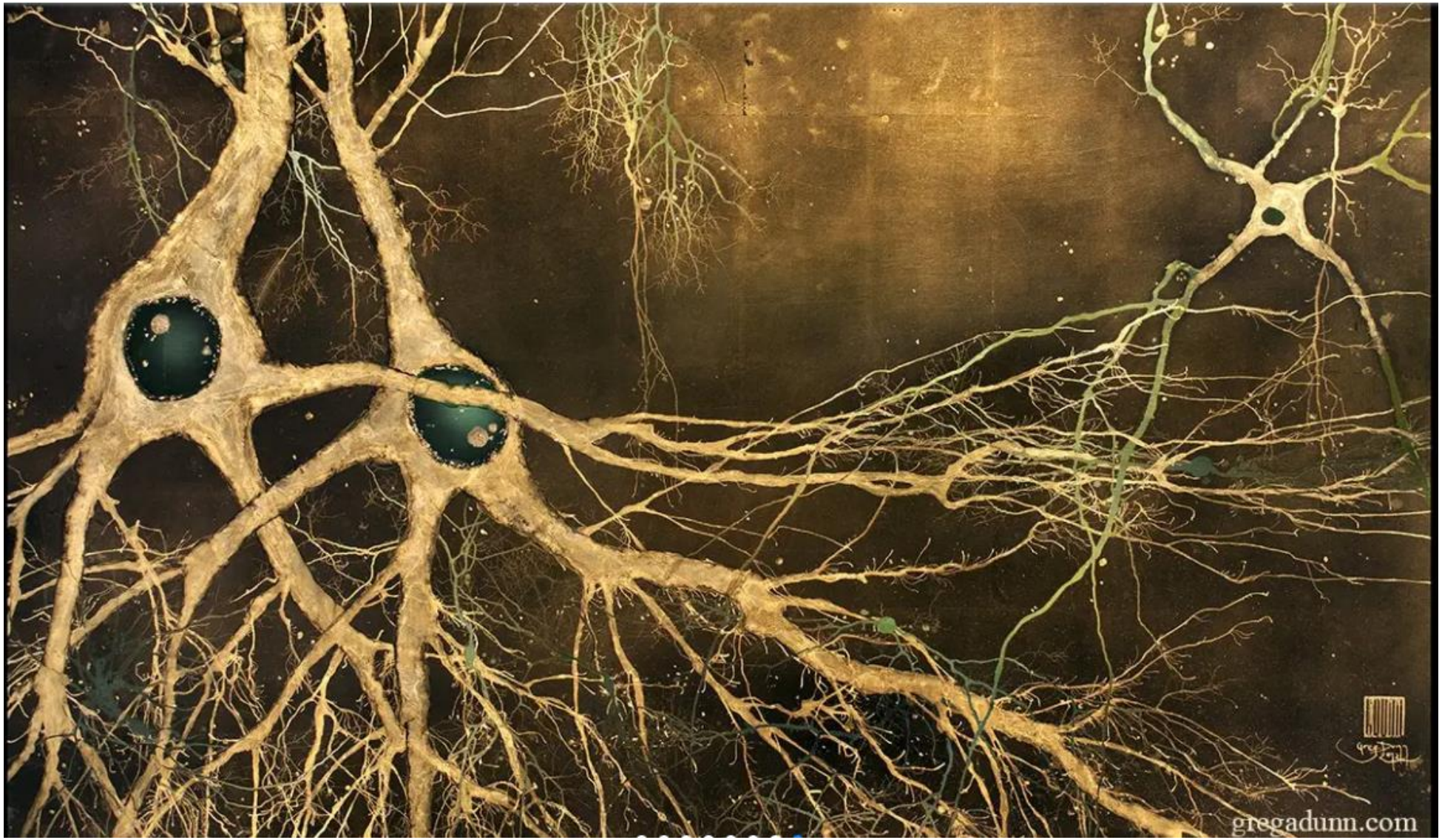
*** Autonomous cars**

*** Some imaging analytics/diagnostics**

*** ChatGPT**


Risk increases
Generative AI
Subset of Deep Learning. A type of Artificial Neural Network that generates data and outputs, without explicit instruction, based on the data it was trained on. Example: LLMs, GANS, etc.
Deep Learning
Subset of ML. Training artificial neural networks on large amounts of data to learn patterns and representations. Once trained, makes autonomous decisions/predictions.
Machine Learning
Creates algorithms that learn from data and make decisions based on observed patterns. [Needs human intervention (currently) / bad at identifying causation]
Artificial Intelligence

Machine Learning & Neural Networks



Machine Learning (neural networks)

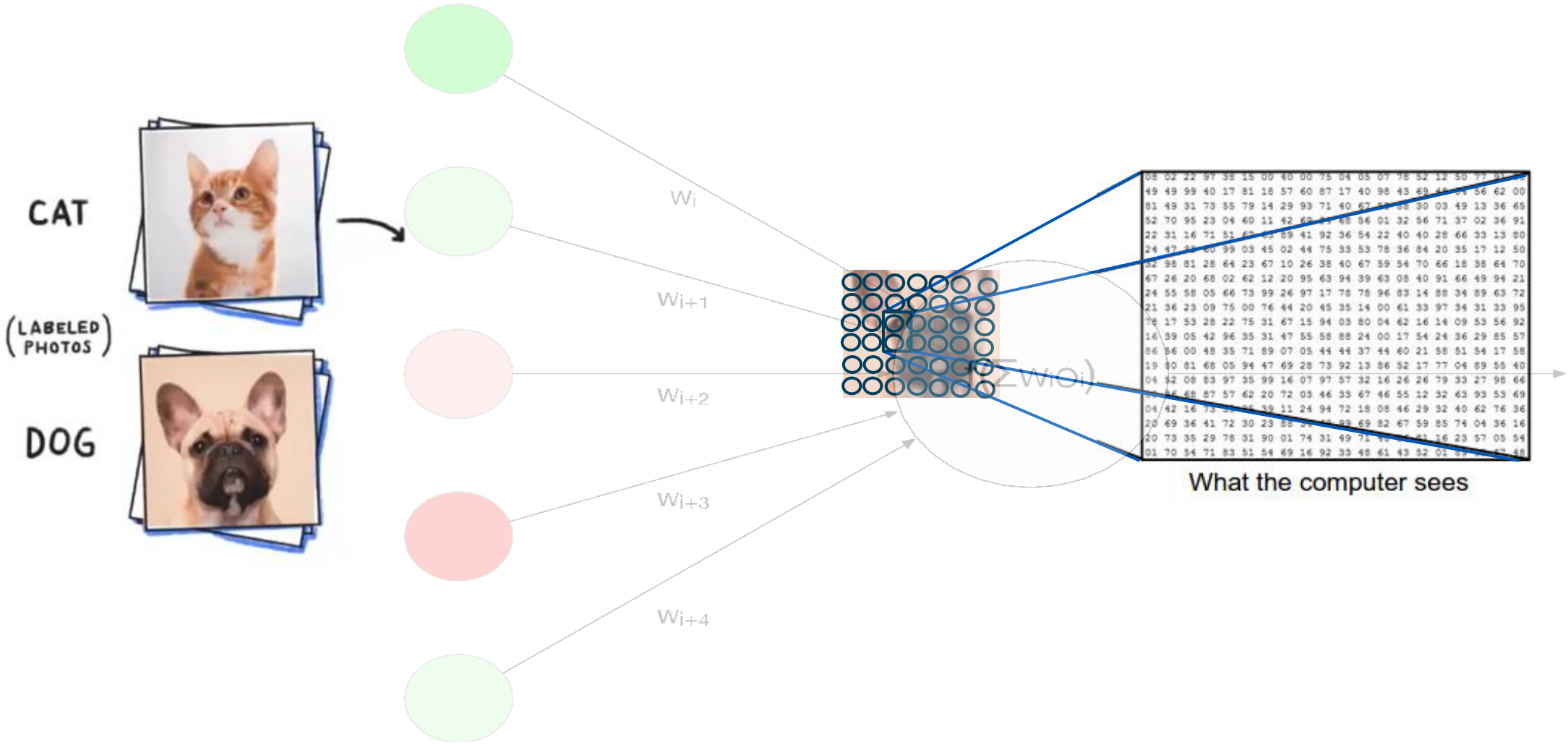


Photo credit: https://buffml.com/image-classification/

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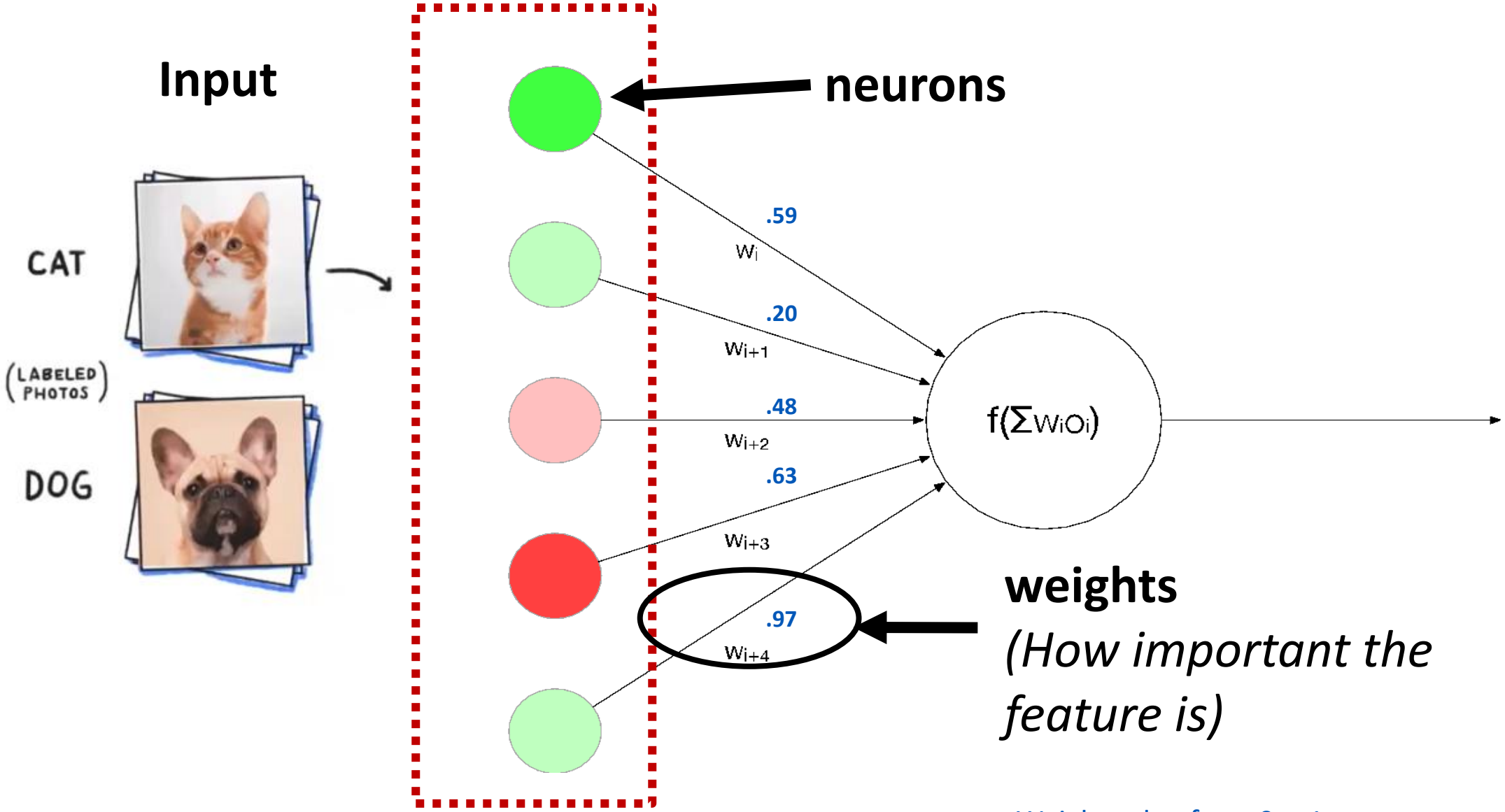
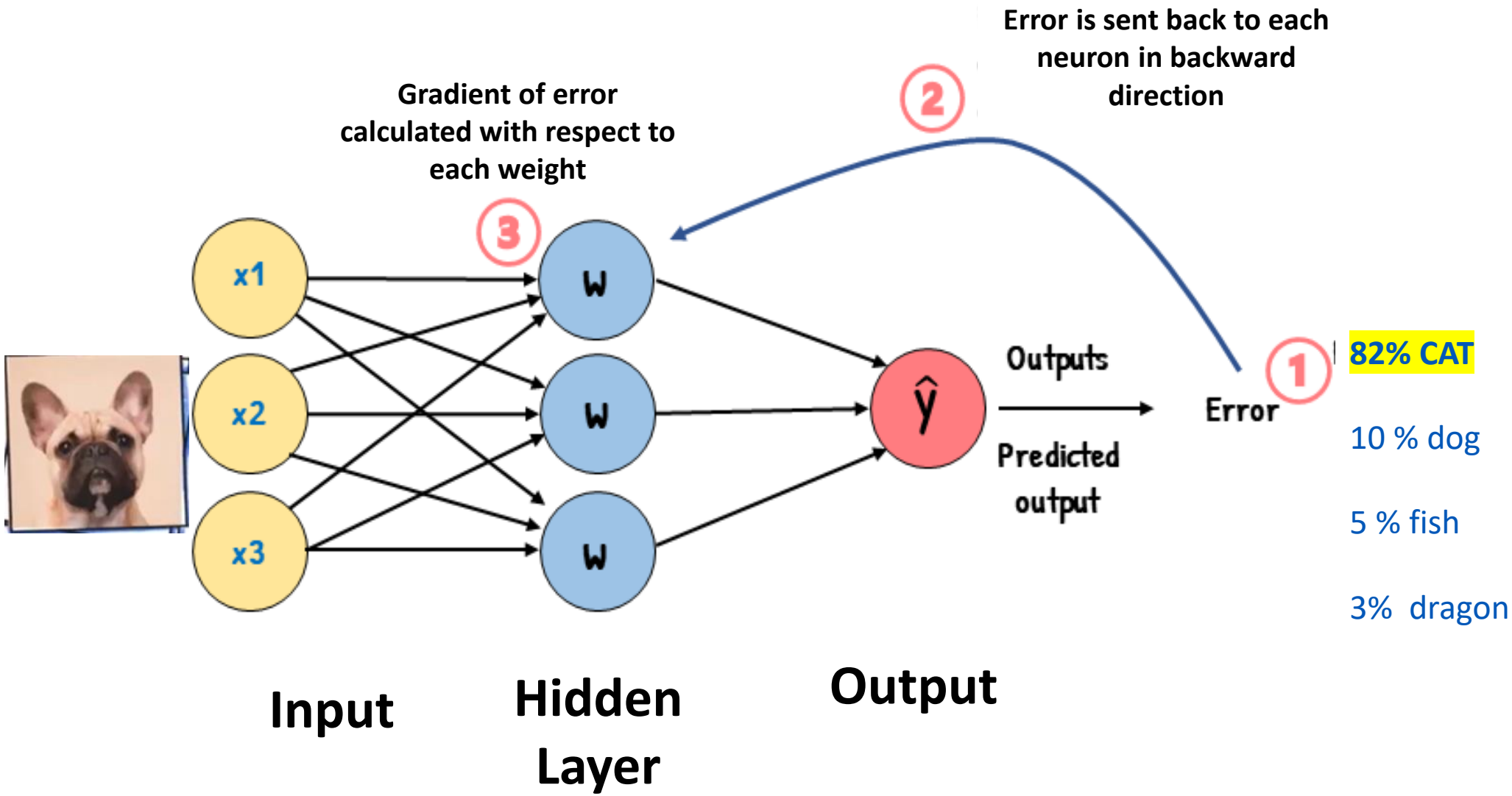


Back Propagation



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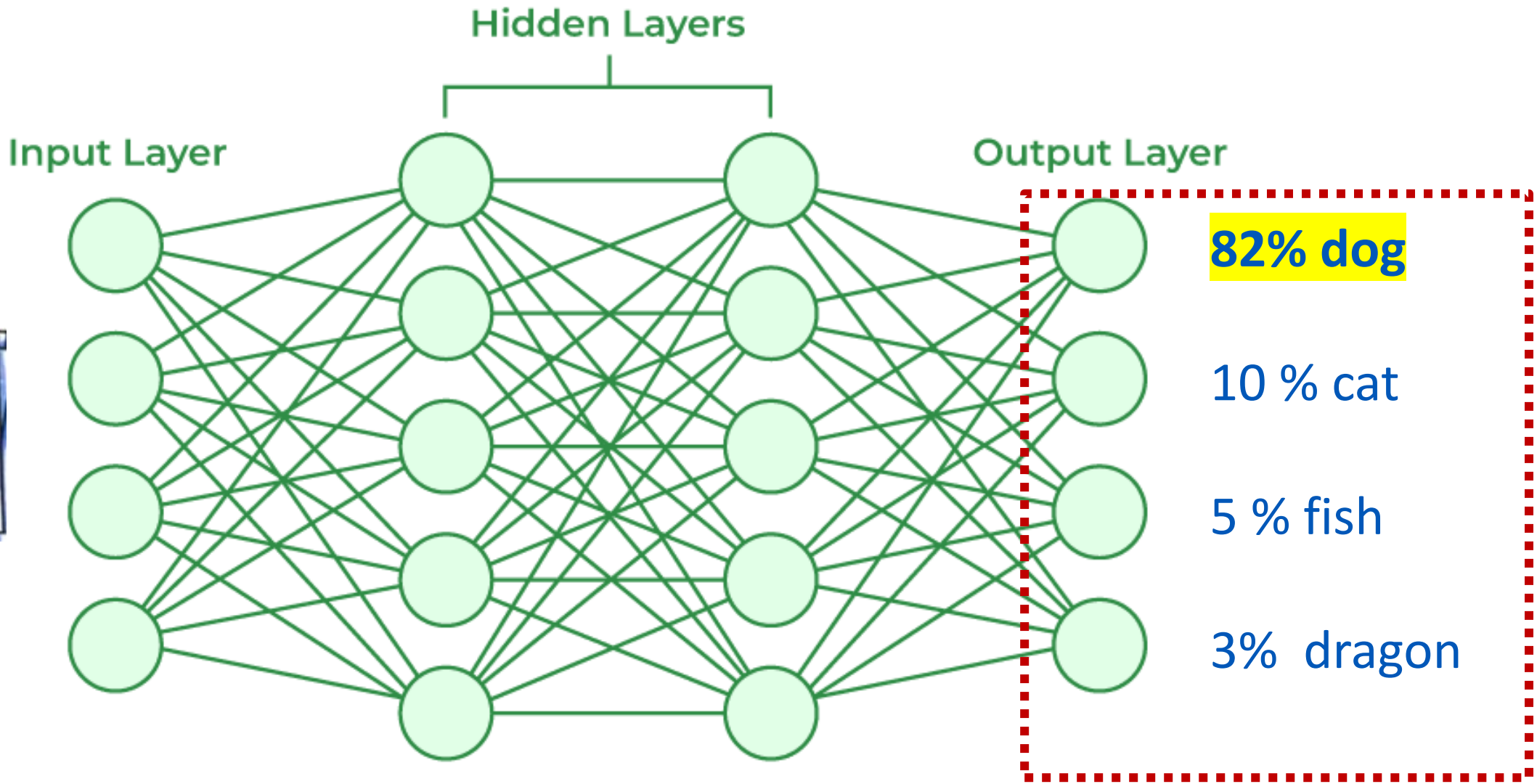

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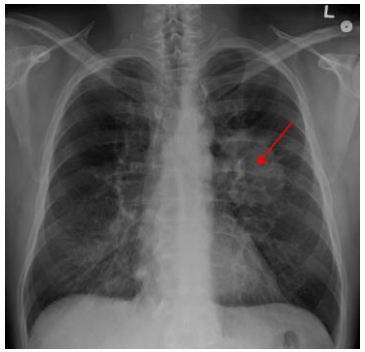


90% malignant tumor

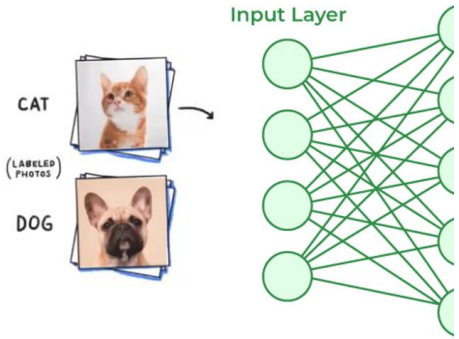
7% benign tumor

2% calcification

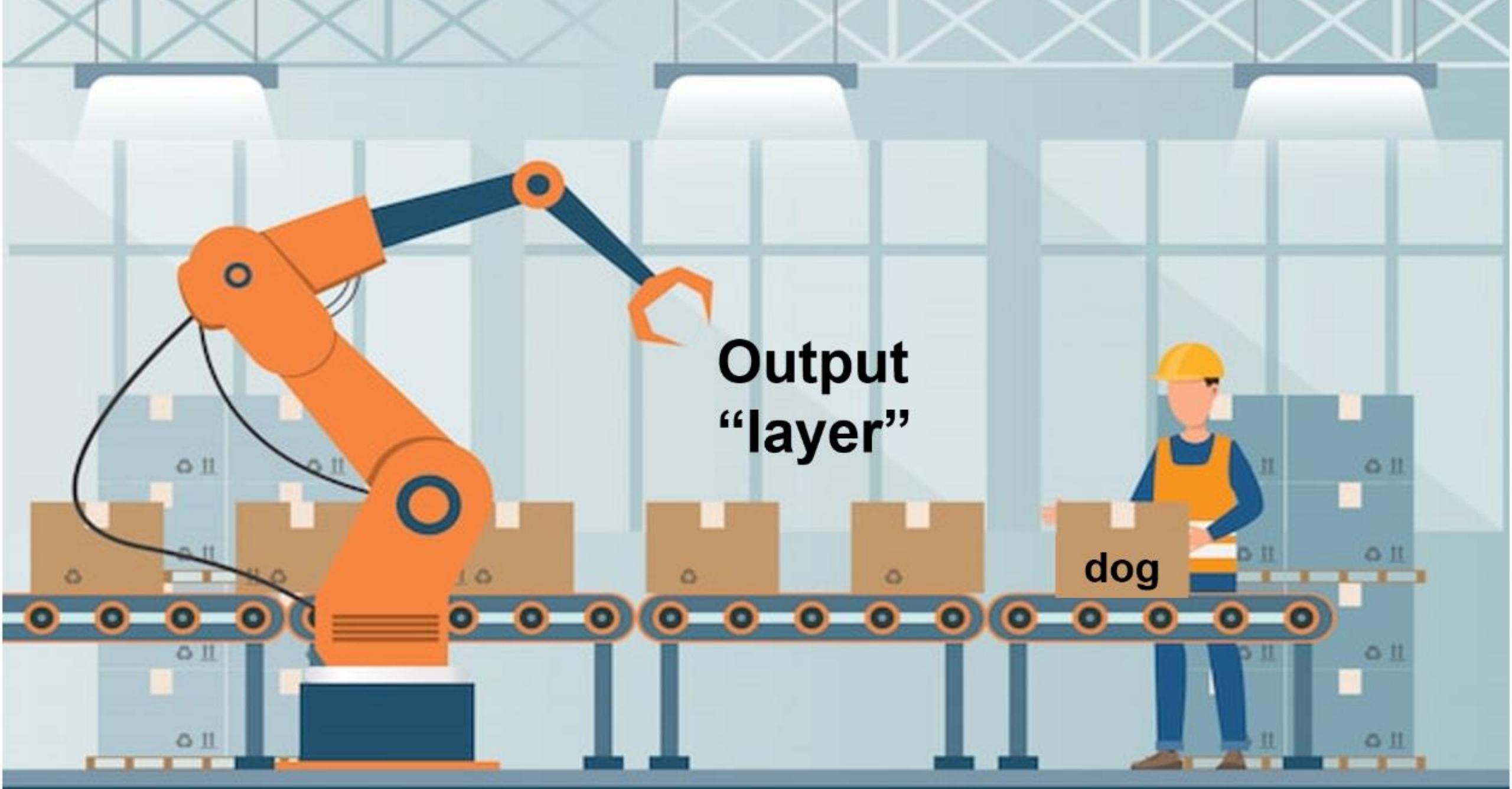
1% other

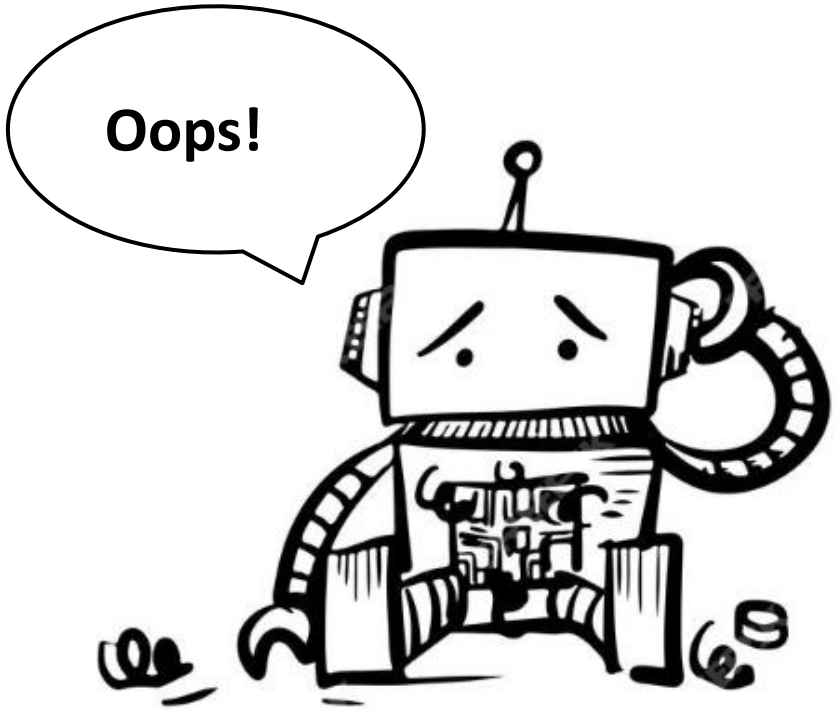
END: Output “layer”

Hidden “layers”



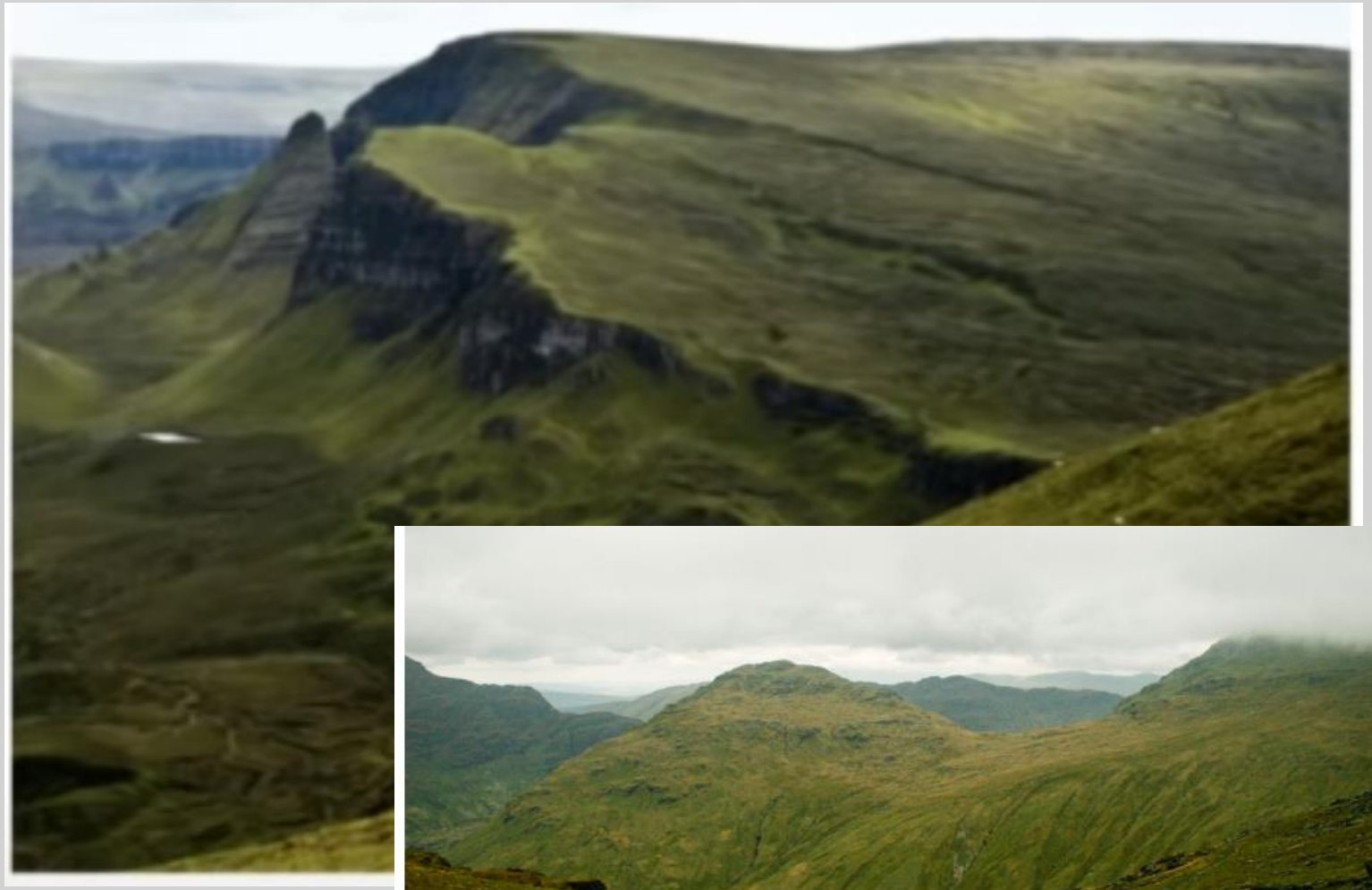
START: Input “layer”


Output
“layer”
dog



AI FAILURES

EXAMPLES OF FAILED AI



A herd of sheep grazing on a lush green hillside
Tags: grazing, sheep, mountain, cattle, horse

https://www.aiweirdness.com/do-neural-nets-dream-of-electric-18-03-02/
https://azure.microsoft.com/en-us/services/cognitive-services/computer-vision/#overview

EXAMPLES OF FAILED AI

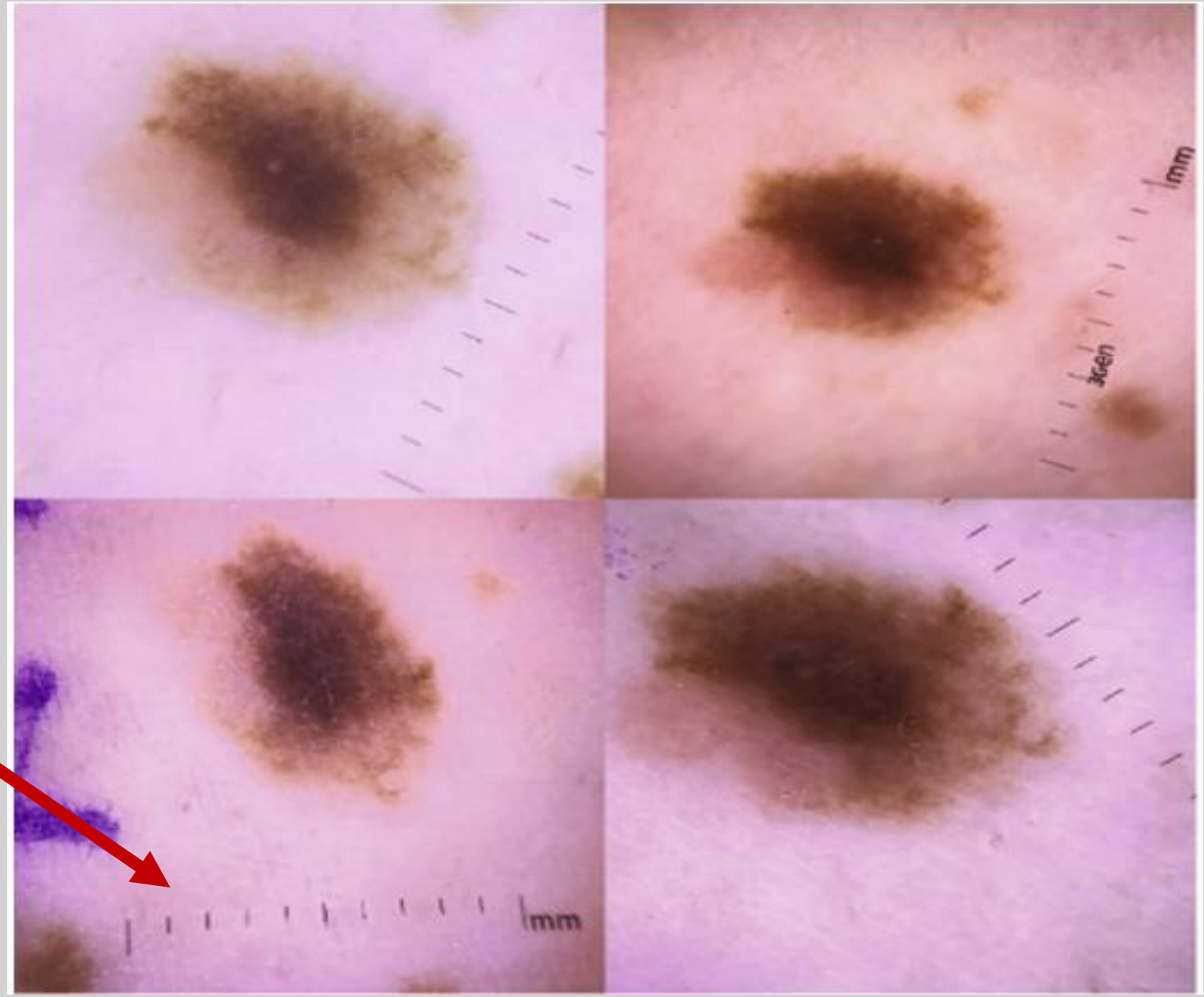
5 13 118

Janelle Shane @JanelleCShane · Mar 1, 2018
"a bird is standing on a tree branch"

1 4 59

Janelle Shane @JanelleCShane · Mar 1, 2018
"a dog and a horse are in a field"

EXAMPLES OF FAILED AI



Narla, A., et al. (2018). Automated Classification of Skin Lesions: From Pixels to Practice. Journal of Investigative Dermatology. Vol. 138. 10. 2108-2110

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POLL TIME!

What do you think?

Poll #1:

If the intent is to build an AI tool to be applied to a broader community ***or*** to data not-yet-collected, this is designed to develop or contribute to "generalizable knowledge" and therefore "research" per the federal definition.

a. True

b. False

Generalizable Knowledge and AI

***NOT* Generalizable AI:**

***-If the intended use of that algorithm is limited to** its application to the original dataset.*

Generalizable AI:

-Intent** is to build a tool to be applied to a broader community **or** to **data not-yet-collected.

-SACHRP (Oct 2022)

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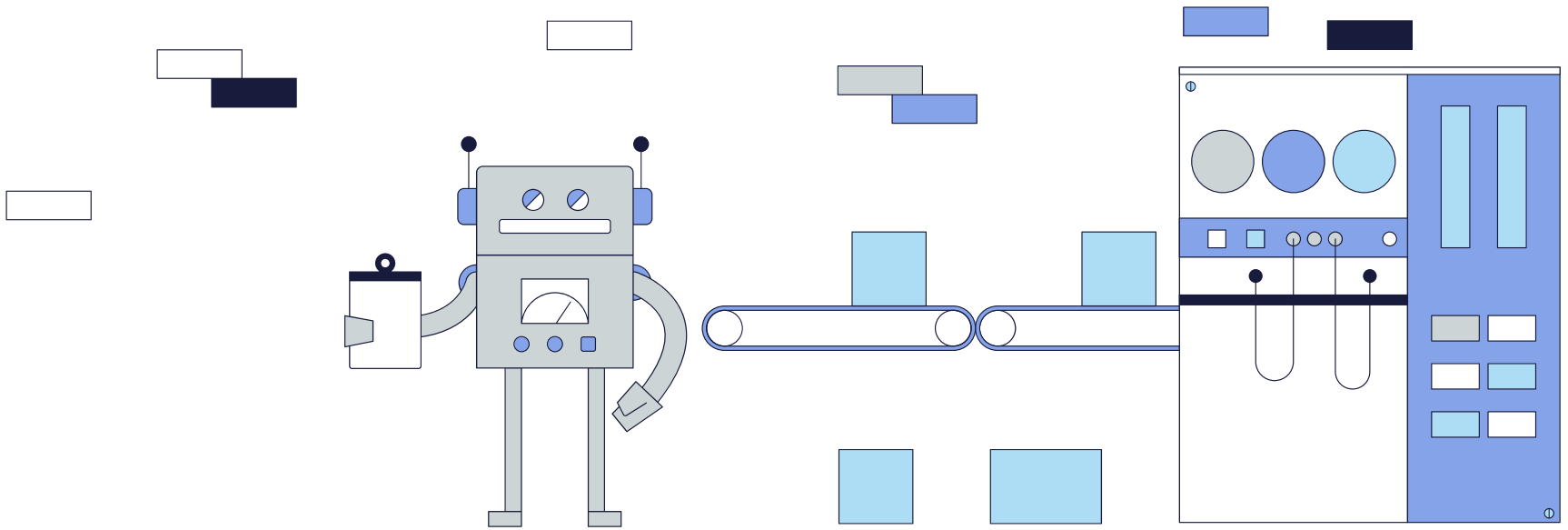


FDA U.S. FOOD & DRUG ADMINISTRATION
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Post
Linkedin
Email
Print
Content current as of:
09/29/2022
Device Software Functions Including Mobile Medical Applications
Examples of Device Software Functions the FDA Regulates
Examples of Software Functions for Which the FDA Will Exercise Enforcement Discretion
Examples of Software Functions That Are NOT
The widespread adoption and use of software technologies is opening new and innovative ways to improve health and health care delivery.
Software functions that meet the definition of a device may be deployed on mobile platforms, other general-purpose computing platforms, or in the function or control of a hardware device. The FDA's policies are independent of the platform on which they might run, are function-specific, and apply across platforms. The term "software functions" includes mobile applications (apps).
Mobile apps can help people manage their own health and wellness, promote healthy living, and gain access to useful information when and where they need it. These tools are being adopted almost as quickly as they can be developed. Users include health care professionals, consumers, and patients.
The FDA encourages the development of mobile medical apps (MMAs) that improve

"Medical Device"

*If a **software function** is intended for use in performing a medical device function (i.e., for **diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease**), it is a medical device, **regardless of the platform on which it is run**.*

https://www.fda.gov/media/80958/download


U.S. FOOD & DRUG ADMINISTRATION
Home / Regulatory Information / Search for FDA Guidance Documents / Policy for Device Software Functions and Mobile Medical Applications
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Policy for Device Software Functions and Mobile Medical Applications
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Search for FDA Guidance Documents
Search General and
FDA Will Exercise
Enforcement Discretion
Examples of Software
Functions That Are NOT
Docket Number:
FDA-2011-D-0530
Issued by:
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
FDA is issuing this guidance to communicate how the Agency intends to apply its
regulatory oversight to certain software, including device software functions and mobile
medical applications (MMAs) intended for use on mobile platforms or on general-purpose
Content current as of:
09/28/2022
Regulated Product(s)
Biologics
Medical Devices
Digital Health

FDA's Approach to Investigational Devices

Investigational Device Exemption (IDE)

CLINICAL EVALUATION

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

Clinical evaluation of devices that have not been cleared for marketing requires:

- an investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
- informed consent from all patients;
- labeling stating that the device is for investigational use only;

Content current as of:
10/03/2022

Regulated Product(s)
Medical Devices

Topic(s)
FDA Activities

POLL TIME!

What do you think?

Poll #2:

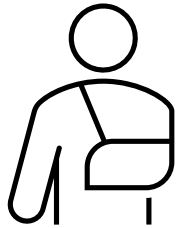
A PI is validating their collaborator's cancer predictive model using only deidentified images and data. This is ***not*** human subjects, and therefore does not require IRB review.

a. True

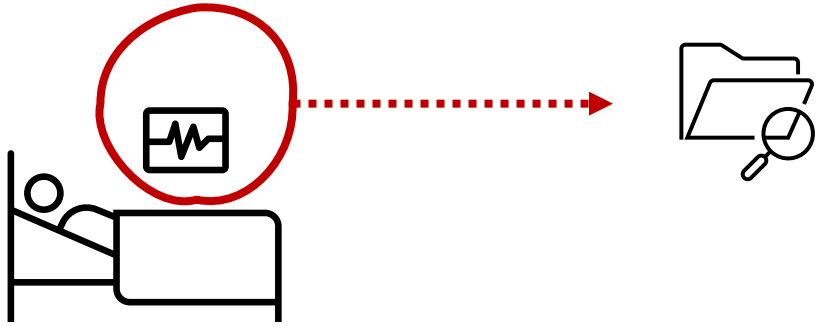
b. False

Two Kinds of “Human Subject”

Human Subject



Human Data Subject



Common Rule

- ✓ Identifiable data
- ✓ May or may not involve interactions/ interventions

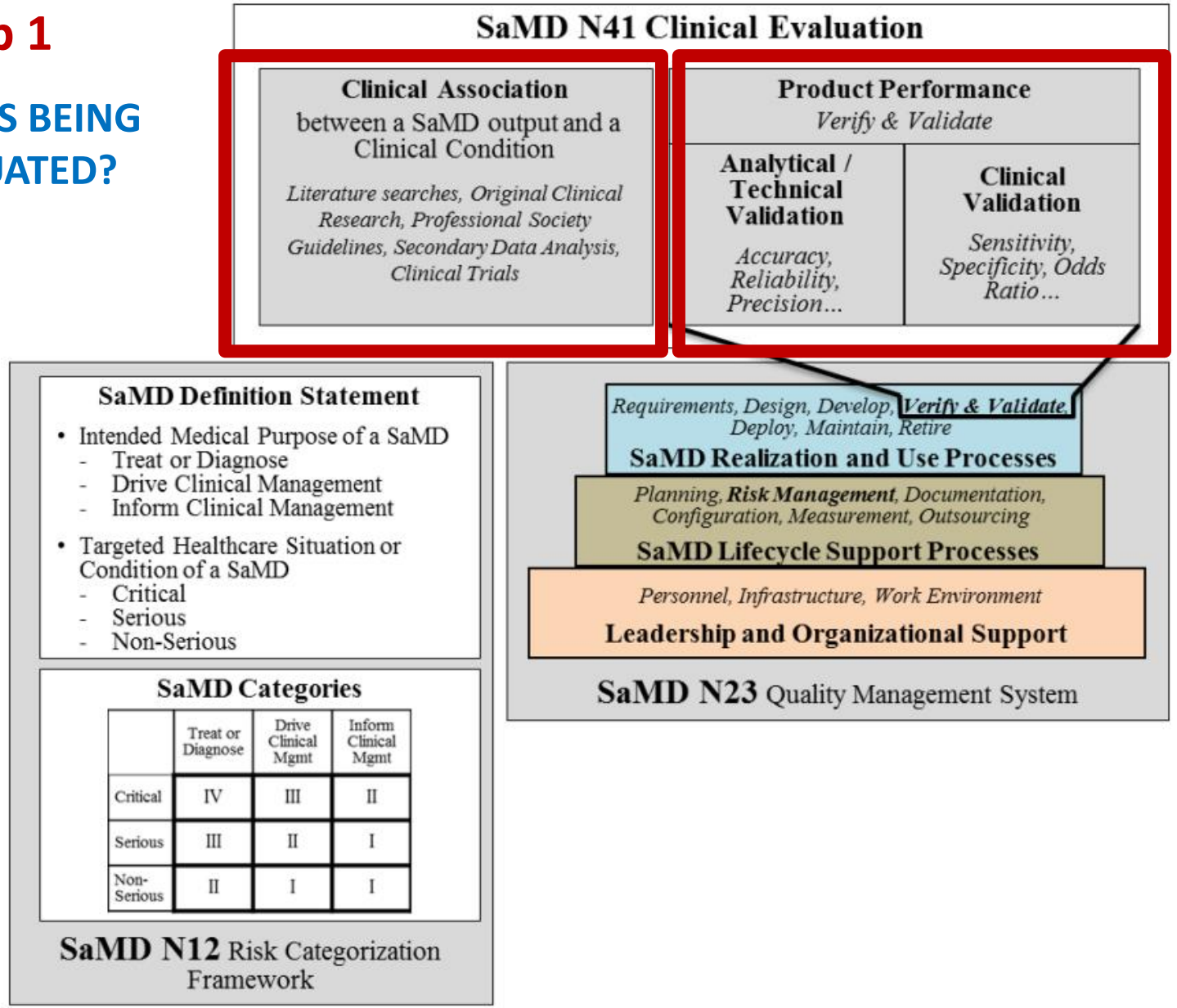
FDA

- ✓ Identifiable ***OR*** deidentified data
- ✓ May or may not involve interactions/ interventions

Clinical Evaluation of Software as a Medical Device (SaMD):

Step 1

WHAT IS BEING EVALUATED?

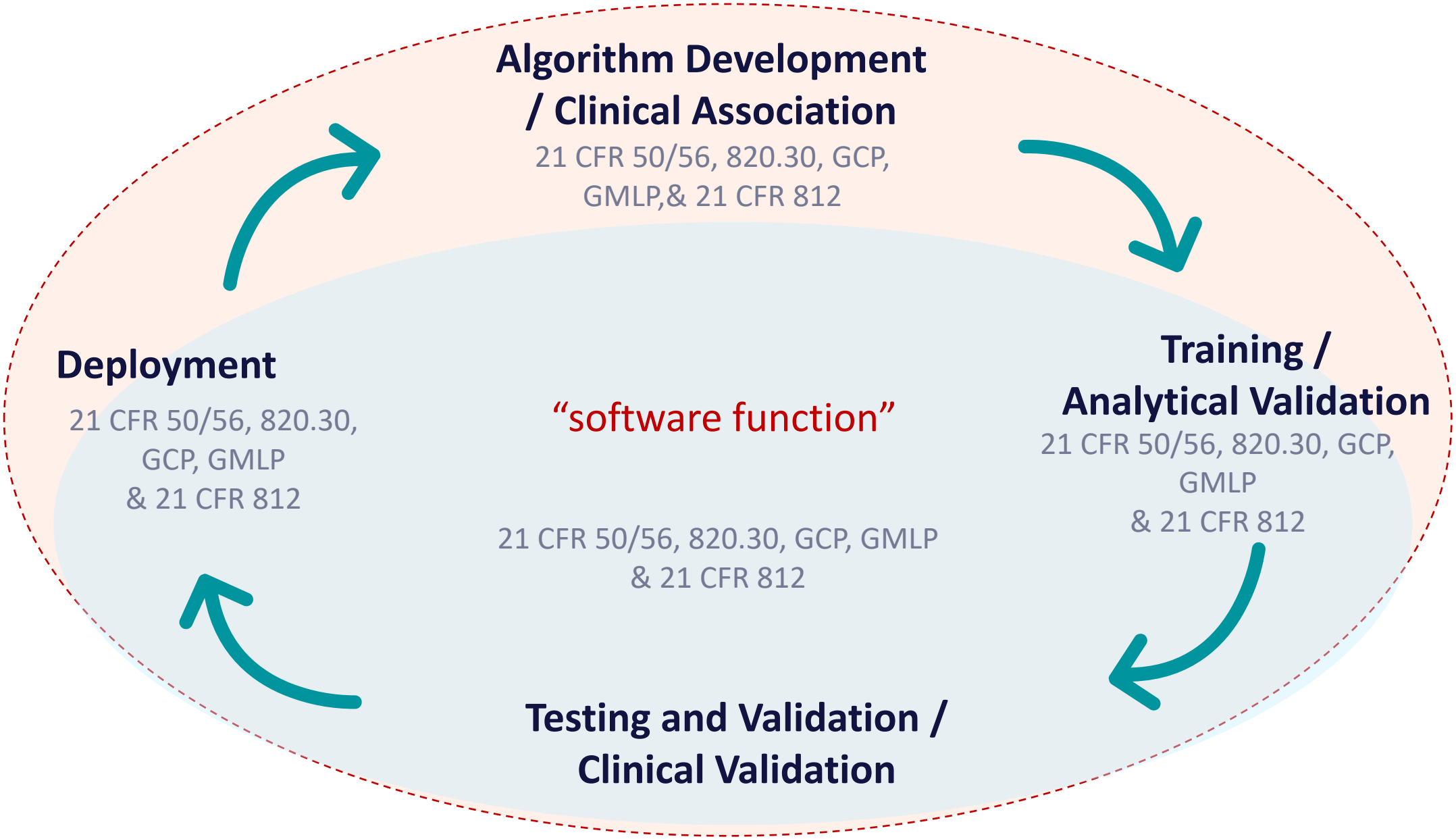


Step 2

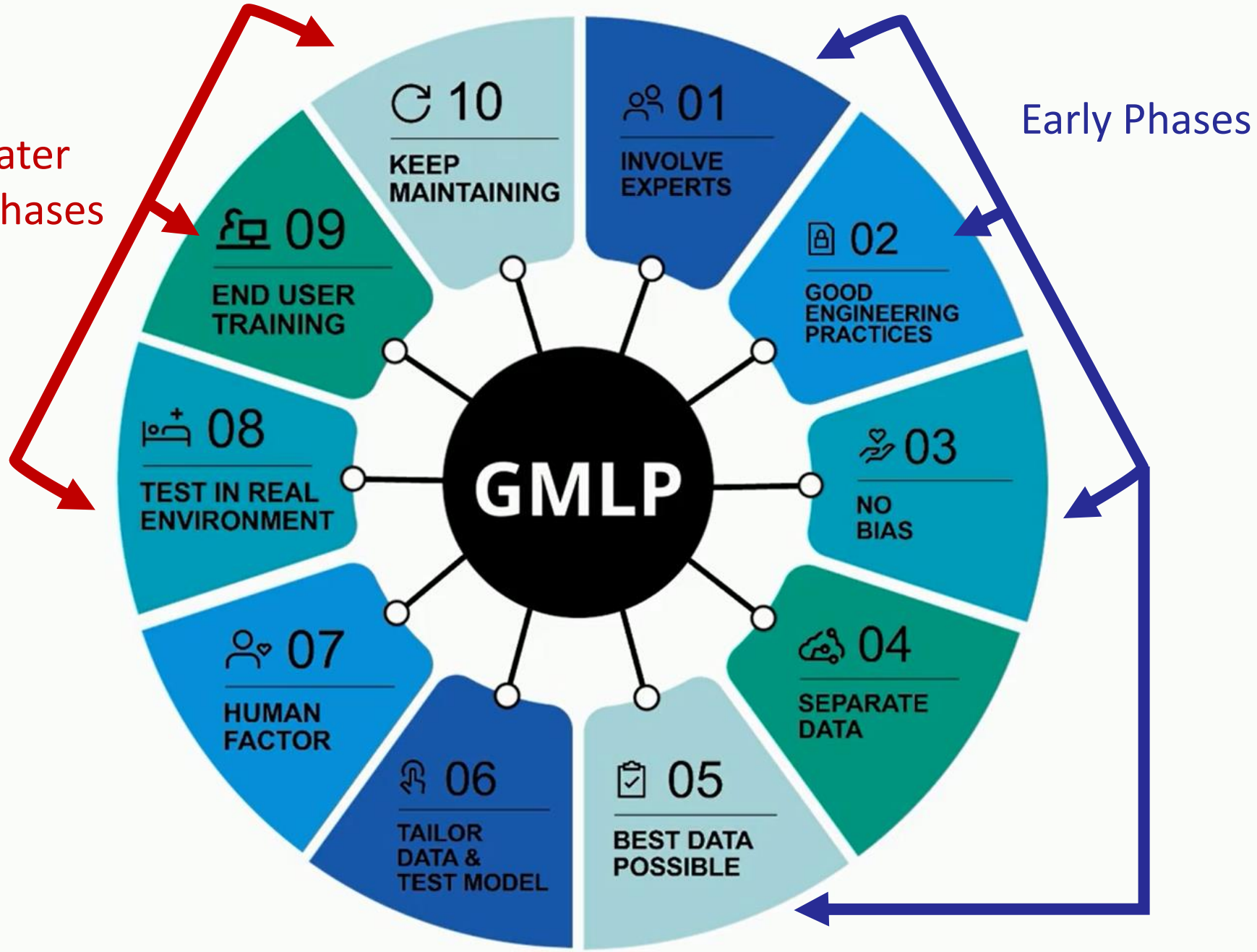
HOW IS IT BEING EVALUATED?

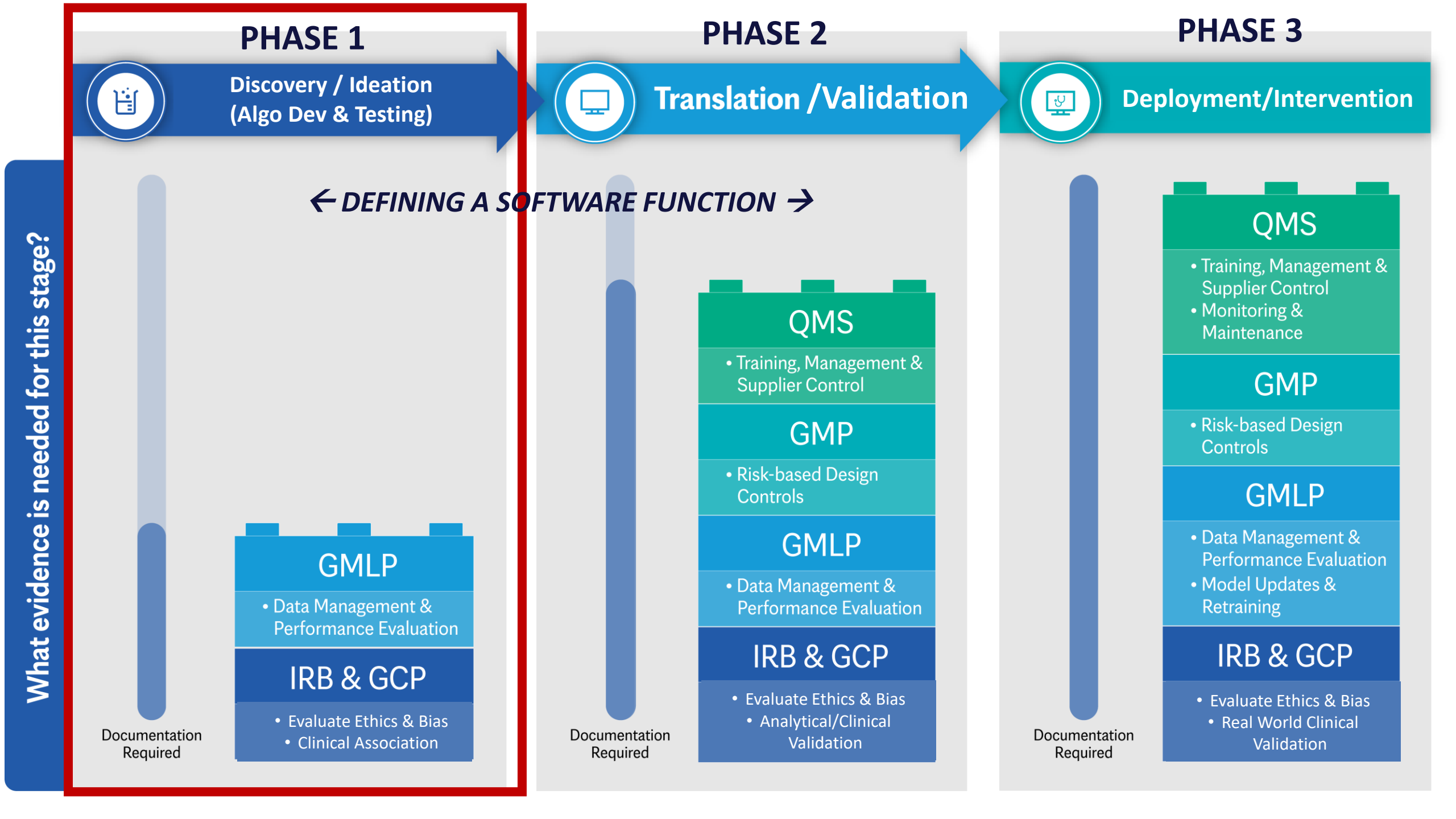
THROUGH FDA & ISO STANDARDS & PROCESSES

WHEN DO FDA REGS KICK IN?



Good Machine Learning Practice (GMLP)




What evidence is needed for this stage?
PHASE 1
Discovery / Ideation
(Algo Dev & Testing)
PHASE 2
Translation /Validation
PHASE 3
Deployment/Intervention
← DEFINING A SOFTWARE FUNCTION →
Documentation Required
GMLP
• Data Management & Performance Evaluation
IRB & GCP
• Evaluate Ethics & Bias
• Clinical Association
Documentation Required
QMS
• Training, Management & Supplier Control
GMP
• Risk-based Design Controls
GMLP
• Data Management & Performance Evaluation
IRB & GCP
• Evaluate Ethics & Bias
• Analytical/Clinical Validation
Documentation Required
QMS
• Training, Management & Supplier Control
• Monitoring & Maintenance
GMP
• Risk-based Design Controls
GMLP
• Data Management & Performance Evaluation
• Model Updates & Retraining
IRB & GCP
• Evaluate Ethics & Bias
• Real World Clinical Validation

WHAT'S NEEDED AT EACH PHASE?

Algorithm Development / Clinical Association

- During the **data selection**, assessment, and management phase, data used for algorithm development should be assessed for biases, **accuracy, fitness** for the intended purpose, and **representativeness** of the intended population.

Training / Analytical Validation

- **Any issues identified should be documented**, and **corrective actions** should be **taken** before moving to algorithm development, training, and validation

Testing and Validation / Clinical Validation

- Algorithms **should be validated across populations** to **ensure fairness** in performance

Deployment

- Performance and **data drift.**
- Assess fairness and equity of algorithm output**, impact** on patients, populations, and society, including data privacy and resource allocation.
- Measure and compare outcomes between advantaged and historically marginalized populations.
- **Continuous Monitoring**

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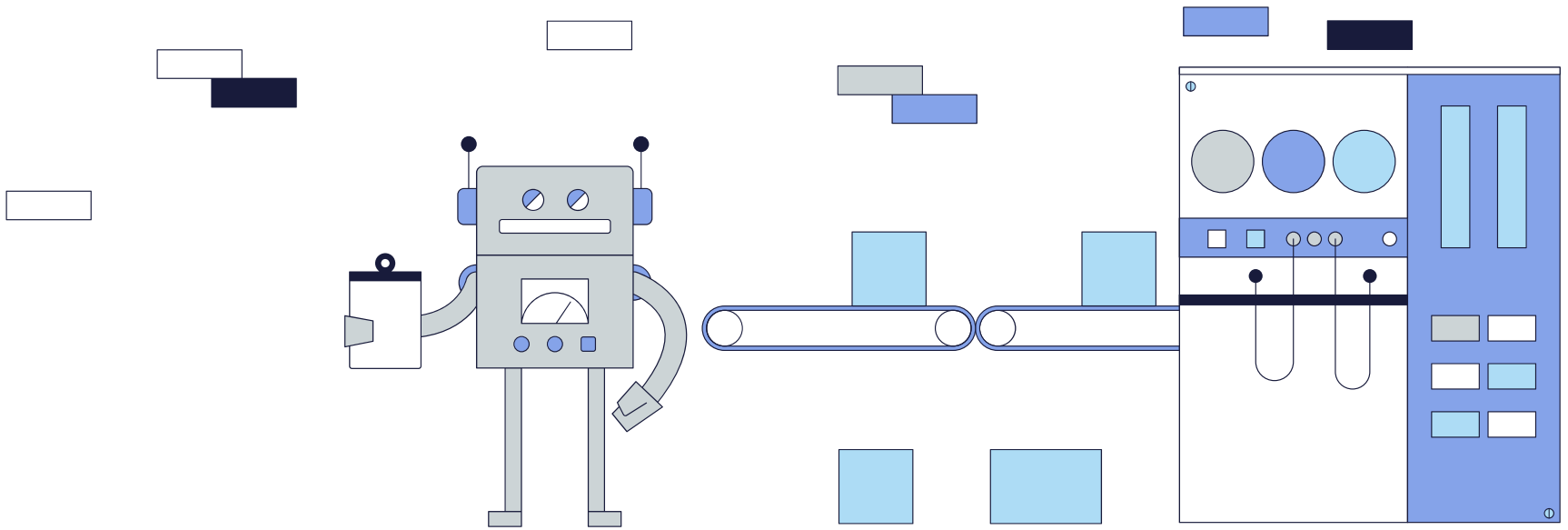


PHASES OF CLINICAL EVALUATION:

Clinical Evaluation

Clinical Association
between software output and clinical condition:
*Literature searches, original clinical research, professional society guidelines, **secondary data analysis**, past clinical trial findings*

Product Performance Verify & Validate

Analytical / Technical Validation
Accuracy, Reliability, Precision...

Clinical Validation
Sensitivity, Specificity, Odds Ratio... (near final)

Clinical Investigation

Clinical Trial (pre-approval)

Pilot: Small study to determine preliminary safety and performance
Pivotal: Larger study to determine efficacy and adverse effects

Clinical Trial (post-approval)

Collection of long-term data on effectiveness, safety & usage

(usually non-interventional)

Phase 1: Exploratory/ Discovery/ Ideation
(pre-clinical)

Phase 2: Pilot/Validation
(early feasibility, preliminary safety & performance)

Phase 3: Intervention/ Interaction/ Treatment
(Confirms clinical efficacy, safety & risks; Potentially impacts patient health, care, or treatment)

PHASES OF CLINICAL EVALUATION:

IDENTIFY THE STUDY AIM

Clinical Eva

Clinical Association
between software output and clinical condition:
*Literature searches, original clinical research, professional society guidelines, **secondary data analysis**, past clinical trial findings*

Phase 1: Exploratory/ Discovery/ Ideation
(pre-clinical)

What is a Clinical Association?

1) **The first phase of Clinical Evaluation**

2) **Typical Study Aims:**

- To determine if there is a valid clinical association between the software function's output, based on the inputs and algorithms selected, and the software function's targeted clinical condition

- Verify that the association between the software function's output and the targeted clinical condition is supported by evidence.

Clinical Association
between software output and clinical condition as indicated by:

- *Literature searches,*
- *Previous original clinical research,*
- *Professional society guidelines,*
- *Generating New Evidence:*
  - ***Secondary data analysis,***
  - ***Past clinical trial findings***

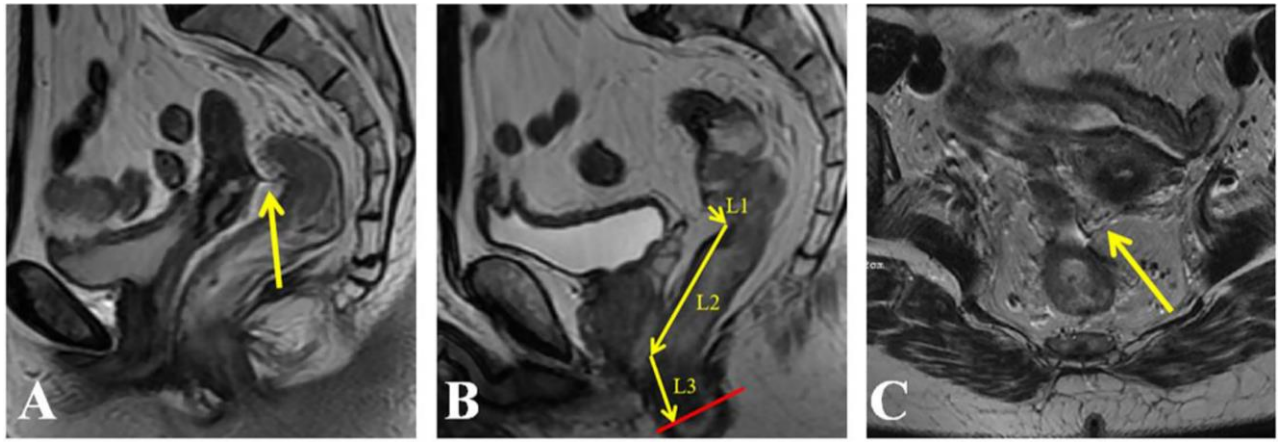
Phase 1:
Exploratory/ Discovery/ Ideation
(pre-clinical; NON-INTERVENTIONAL)

Phase 1 – Clinical Association

- ✓ Non-interventional (Retrospective Chart Review)
- ✓ Primary objective is to collect data solely for exploratory research purposes, with **no intention of deploying** in real environments [such as medical records].
- ✓ **NO ANALYTICAL OR CLINICAL VALIDATION**- These limitations must be clearly spelled out in the IRB application/ template/protocol
- ✓ Verifies the algorithm correctly processes input data; predictions align with ground truth labels; assesses robustness of model to variations in input data. If proposal meets ALL the above, but ALSO includes **validation**, process as Phase 2 (Analytical/Clinical Validation) and consider device risk determination (SR/NSR))

PHASE 1: EXPLORATORY/ DISCOVERY/ IDEATION *(PRE-CLINICAL)*

- **AIM:** to develop MRI-based deep learning methods to create AI modules that integrate clinical, genomic, and imaging biomarkers for accurate prediction of post neoadjuvant response, and to improve outcomes in patients with advanced rectal cancer.



- The current study will only conduct **algorithm development** with **training and testing of the algorithm** using retrospective datasets.
- *"In the future, we plan to validate the algorithm. We will submit a modification to include the algorithm as a device in the IRB application and request approval prior to conduct validation."*

PHASES OF CLINICAL EVALUATION:

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between software output and clinical condition:
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(pre-clinical)

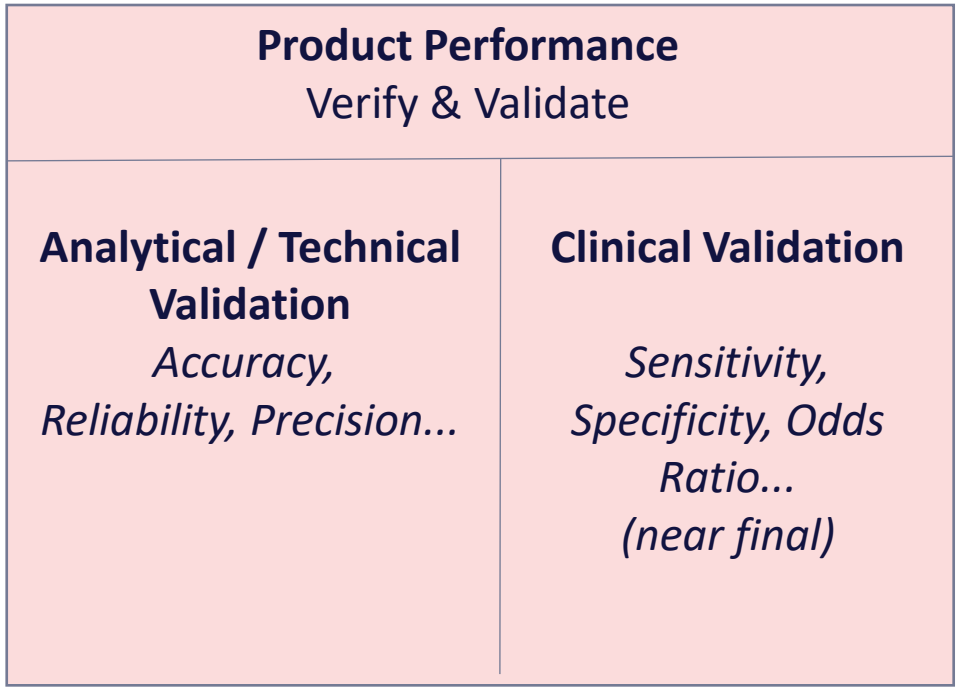
Phase 2: Pilot/Validation
(early feasibility, preliminary safety & performance)

Phase 3: Intervention/ Interaction/ Treatment
(Confirms clinical efficacy, safety & risks; Potentially impacts patient health, care, or treatment)

What is Analytical / Clinical Validation?

Phase 2 of Clinical Evaluation

- **Typical Study Aims:** To determine if the software function meets technical requirements (QSM)
- Generate evidence that shows output is *technically* what was expected (non-interventional) for intended use and will *likely* achieve clinically meaningful outcomes through predictable and reliable use.
- Verify that specified requirements (ISO, FDA, etc.) have been fulfilled. **Confirm the requirements for a specific intended use or application have been fulfilled.**



Phase 2: Pilot/Validation

(early feasibility, preliminary safety & performance)

NOTE: *Post-market, Clinical Evaluation is a continuous process throughout the software's life-cycle done under QA*

Phase 2- Validation

- Prospective validation (must be on a DIFFERENT data set than what was used for Phase 1); **AND**

- **Non-interventional** (**DOES NOT IMPACT SUBJECT/PATIENT CARE**); **AND**
  - Technology tested **CANNOT** influence treatment recommendations, study eligibility or randomization into a specific study arm, or alter the standard of care. **AND**

- **Off-Line:** Output must not be placed in medical records or live clinical environments.
  - If output is entered into EMR ("deployed"), **not IDE-Exempt eligible**. A NSR/SR device risk determination must be made by the IRB (or FDA). This is done by evaluating software functionality and hazard mitigation strategies.

- **Analytical/Clinical Validation studies:**
  - **Examples:** Testing performance with the intent to *demonstrate deployment capability* in clinical setting (such as assessing how well algorithm performs in diagnosing a specific type of cancer).

- Limitations of study must be clearly spelled out in the IRB application/protocol/Approval Letter.

- FDA regulations (21 CFR 812, 809, 820.30) may apply

PHASE 2: PILOT/VALIDATION (DEFINED SOFTWARE FUNCTION)
(EARLY FEASIBILITY, PRELIMINARY SAFETY & PERFORMANCE)

- **AIM:** Evaluate CHiRP accuracy on images that were obtained in a department that uses ultrasound equipment that ChiRP has not yet been exposed to or trained on.
- **Software Function:** Collection of models trained on images from cardiothoracic ultrasounds.

- **Classifiess images** qualitatively (normal/abnormal) and quantitatively (continuous numerical values).
- *"We will compare the product's performance compared to the radiologist's manual evaluation. All output and observations will be held on a research server and will not be entered into EMR or Epic)"*

PHASES OF CLINICAL EVALUATION:

Clinical Evaluation

Clinical Association
between software output and clinical condition:
*Literature searches, original clinical research, professional society guidelines, **secondary data analysis**, past clinical trial findings*

Product Performance
Verify & Validate

Analytical / Technical Validation
Accuracy, Reliability, Precision...

Clinical Validation
Sensitivity, Specificity, Odds Ratio... (near final)

Clinical Investigation

Clinical Trial (pre-approval)

Pilot: Small study to determine preliminary safety and performance
Pivotal: Larger study to determine efficacy and adverse effects

Clinical Trial (post-approval)

Collection of long-term data on effectiveness, safety & usage

(usually non-interventional)

Phase 1: Exploratory/ Discovery/ Ideation
(pre-clinical)

Phase 2: Pilot/Validation
(early feasibility, preliminary safety & performance)

Phase 3: Intervention/ Interaction/ Treatment
(Confirms clinical efficacy, safety & risks; Potentially impacts patient health, care, or treatment)

What is A Clinical Investigation?

Phase 3 of Clinical Evaluation

- a.k.a. "clinical trial" or "clinical study"
- Potentially impacts research participant/patient health, care, or treatment
- **Research Question:** what works and doesn't work in treating humans
- Establish/verifies safety, device performance, benefits, and effectiveness
- Must meet standards and regulations (ISO, applicable FDA regulations, etc.)

Clinical Investigation

Clinical Trial (pre-approval)	**Clinical Trial (post-approval)**
Pilot: Small study to determine preliminary safety and performance **Pivotal:** Larger study to determine efficacy and adverse effects	Collection of long-term data on effectiveness, safety & usage (usually non-interventional)

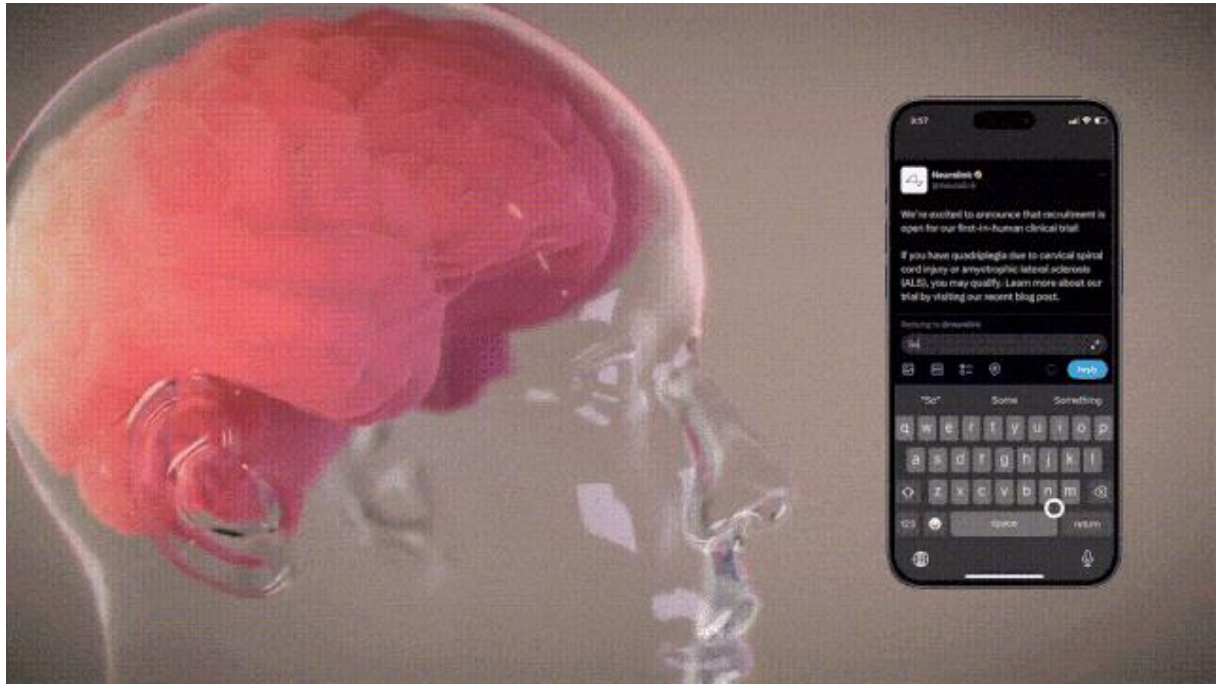
Phase 3: Intervention/ Interaction/ Treatment
(Confirms clinical efficacy, safety & risks)

Phase 3: Intervention or Interaction

- *Clinical Investigation, Clinical Study, or Clinical Trial*
- Uses software function in real environments (e.g., electronic medical records, or in interventional/interaction scenarios).
- **Projects either:**
  - (a) involve interaction with patients/study participants, or
  - (b) a healthcare provider might be exposed to the outputs prior to delivering the standard of care.
- **A device risk determination (SR/NSR) must be carefully considered by the IRB (or FDA). This is done by evaluating software functionality and hazard mitigation strategies.**

PHASE 3: INTERVENTION/ INTERACTION/ TREATMENT
(CONFIRMS CLINICAL EFFICACY, SAFETY & RISKS; POTENTIALLY IMPACTS PATIENT HEALTH, CARE, OR TREATMENT)

Neuralink Clinical Trial: PRIME Study: Precise Robotically Implanted Brain-Computer Interface



AIM: Evaluate:

a) the safety of implant,
b) Safety of surgical robot, and
c) Assess the initial functionality of BCI for enabling people with quadriplegia to control external devices with their thoughts.

POLL TIME!

What do you think?

Poll #3:

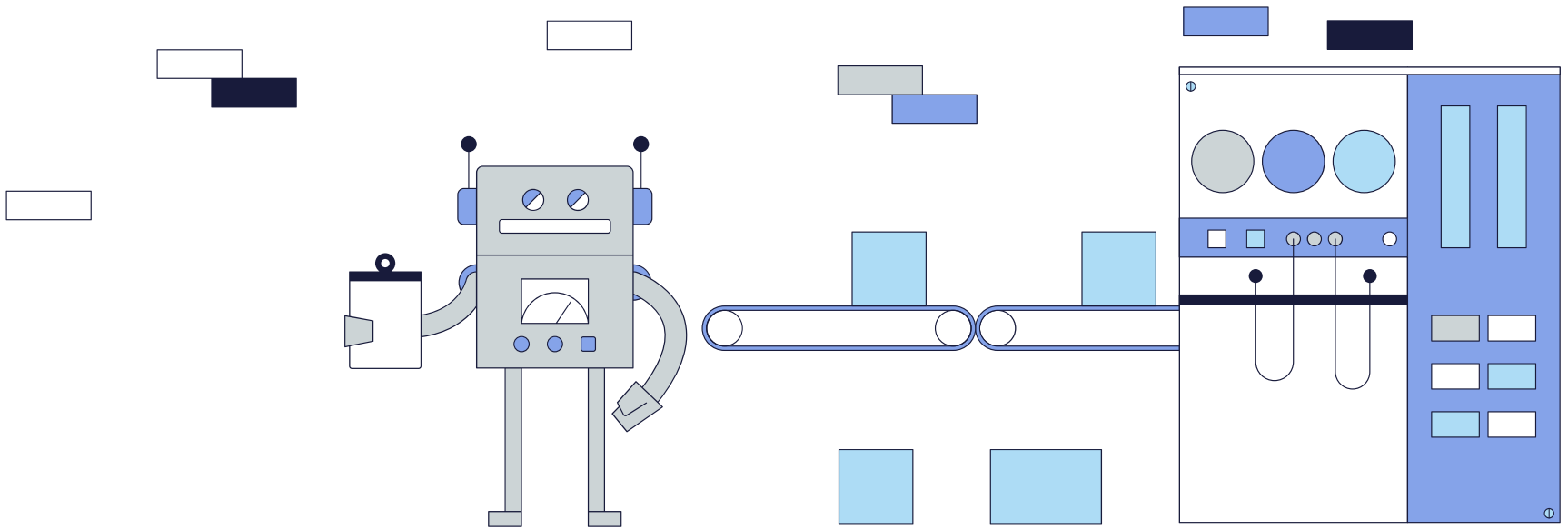
For a study limited to a chart review using AI tools with no interventions, which of the following harms can occur to an individual who is ***only*** participating as a “human data subject” (data contributor)?

a. Privacy and confidentiality breach
b. Harm from false positive or negative results
c. Harm from future misapplication of the tool or output
d. Dignitary harm from involvement w/o consent (learning post-hoc of data being used)
e. Only A and D
f. All the above

Learning Objectives

1. **Demystifying AI**
2. **A Long History of Regulating Software Functions**
3. **Simplifying AI IRB Review: A 3-Phased Approach**
4. **REGULATORY GREY AREAS**

   Recommendations for Navigation

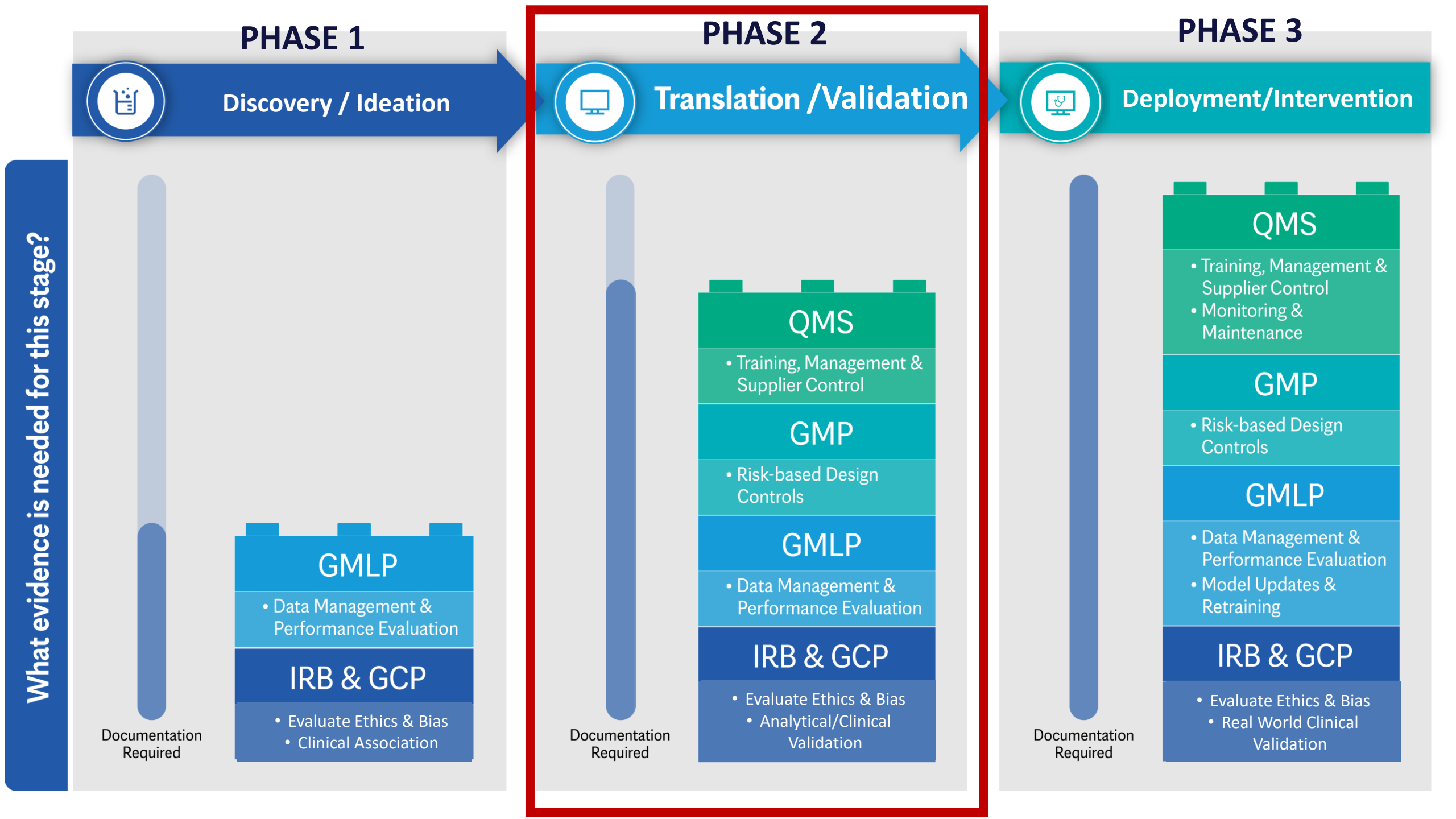


IF THE IRB DETERMINES THE SOFTWARE FUNCTION WAS "NOT A DEVICE" BECAUSE...:

...FUNCTION IS NOT DESIGNED TO SERVE A MEDICAL PURPOSE (ANY PHASE): → FDA regulations do not apply. Process via **45 CFR 46** per standard procedure.

HAS AN INTENDED MEDICAL PURPOSE FUNCTION BUT ELIGIBLE FOR CURES ACT (CDSS) (PHASE 2 *OR* 3): → FDA regulations do not apply. Process via **45 CFR 46** and require Continuing Review under 21 CFR. See here

...STUDY LIMITED TO CLINICAL ASSOCIATION: (EXPLORATORY ONLY/PHASE 1) → FDA regulations may apply. Process via **45 CFR 46** and **21 CFR 56** and require Continuing Review under 21 CFR. Re-evaluate at Phase 2.


What evidence is needed for this stage?
PHASE 1
Discovery / Ideation
Documentation Required
GMLP
• Data Management & Performance Evaluation
IRB & GCP
• Evaluate Ethics & Bias
• Clinical Association
PHASE 2
Translation /Validation
Documentation Required
QMS
• Training, Management & Supplier Control
GMP
• Risk-based Design Controls
GMLP
• Data Management & Performance Evaluation
IRB & GCP
• Evaluate Ethics & Bias
• Analytical/Clinical Validation
PHASE 3
Deployment/Intervention
Documentation Required
QMS
• Training, Management & Supplier Control
• Monitoring & Maintenance
GMP
• Risk-based Design Controls
GMLP
• Data Management & Performance Evaluation
• Model Updates & Retraining
IRB & GCP
• Evaluate Ethics & Bias
• Real World Clinical Validation

What Regs Apply to my Medical Device software function?

IDE-Exempt Studies

21 CFR §50, 56, 809.10(c)(2), 820.30 & Part 11

NOTE: Not eligible for Common Rule “Exempt 4” (45 CFR 46.104)

What Regs Apply to my Medical Device software function?

IDE-Exempt Studies

21 CFR §50, 56, 809.10(c)(2), 820.30 & Part 11

NOTE: Not eligible for Common Rule "Exempt 4" (45 CFR 46.104)

Non-Significant Risk (NRS)

21 CFR §50, 56, 820.30, + abbreviated 812 & Part 11

NOTE: Not eligible for Common Rule "Exempt" Cat. 4 (45 CFR 46.104); Possibly eligible for "Expedited" 1 or 9

NOTE: Requires Full Board review for determination

What Regs Apply to my Medical Device software function?

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21 CFR §50, 56, 809.10(c)(2), 820.30 & Part 11

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21 CFR §50, 56, 820.30, + abbreviated 812 & Part 11

NOTE: Not eligible for Common Rule "Exempt" Cat. 4 (45 CFR 46.104); Possibly eligible for "Expedited" 1 or 9

NOTE: Requires Full Board review for determination

Significant Risk

21 CFR §50, 56, 812, 820, & Part 11
(and more)

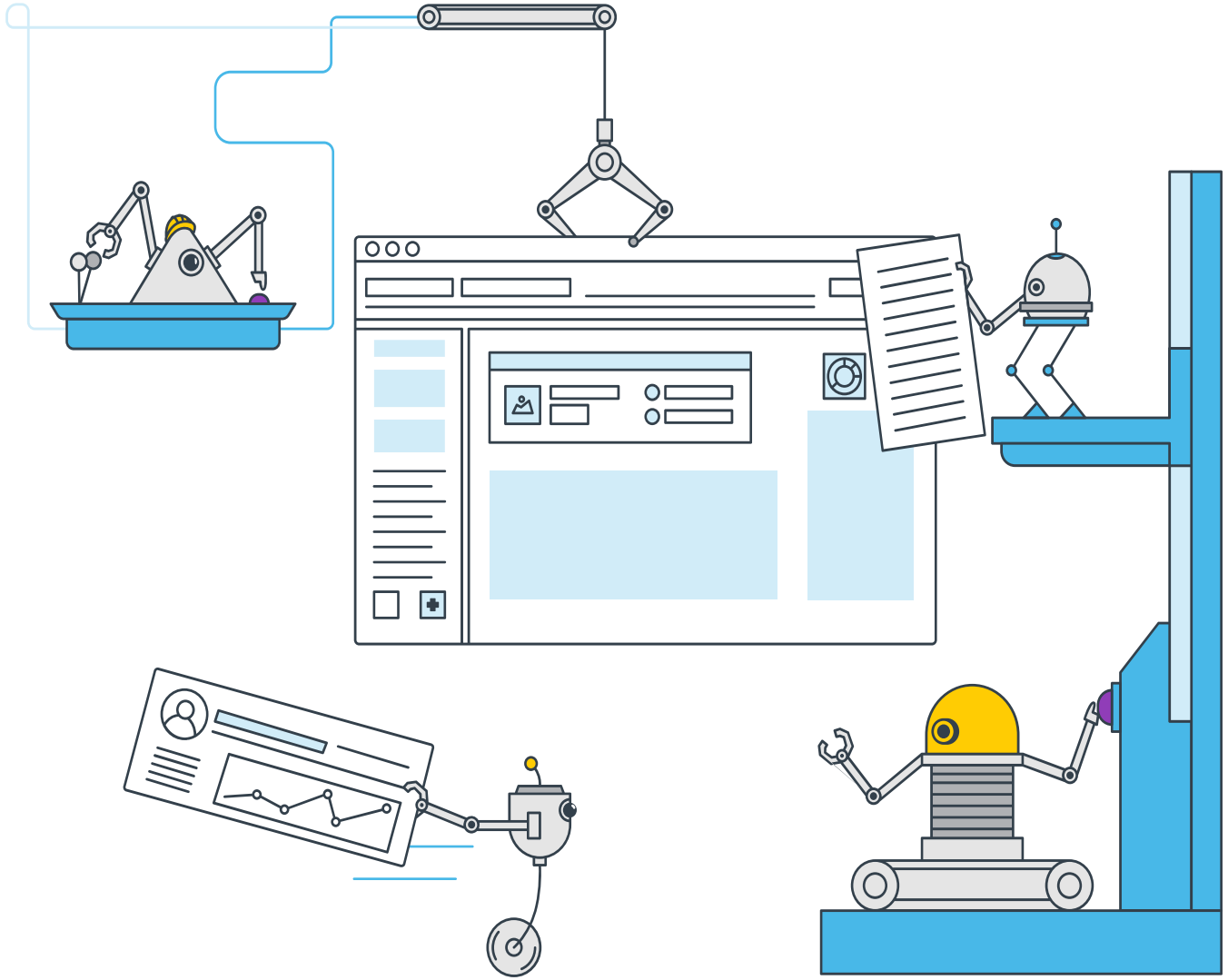
Full Board review

Thank you.

Contact with any questions

Tamiko Eto
Director, Research Operations
HRPP & IRB
Mayo Clinic

Eto.Tamiko@mayo.edu



REGULATORY GAPS

Demonstrating clinical evidence of safety and effectiveness

FDA 510(k)

Gap: Premarket Notification Pathway does not require clinical evidence. 11% are recalled.

Clinical Validation

Gap: Publications often considered as clinical evidence

Misuse & Omittance of "AI"

Gap: Saying AI used when it isn't. Not saying AI is used when it is.

Deployment Pathways (tested & untested product)

Gap: Poor institutional awareness and inventory of deployed AI

Quality Improvement using Untested Products

Gap: Measuring outcomes of AI software functions is not QI

Labeling / Model Cards

Gap: Poor transparency and relevant information provided to end user

Internationally & Legally Sourced Data

GAP: Knowing where your data comes from; Capturing foreign data without authorization or out of compliance.

Understanding PHI and HIPAA

GAP: Lack of proper deidentification and failure to execute DUAs

ADDENDUM

BASIC IRB REVIEW

(The Bare Minimum)

45 CFR 46.111

IRB Confirms Criteria for approval met (45 CFR 46.111 / 21 CFR 56.111)

BENEFICENCE

Risk/Benefit Analysis (2)

Data Safety (6)

Experimental Design (1i)

JUSTICE

Subject Selection (3)

(Inclusion/Exclusion & Recruitment)

RESPECT FOR PERSONS

(a) Informed consent (.117) or
(b) IRB waiver obtained and documented (as appropriate) (.116(e)(f))
(4,5)

Consent/Parent Consent/Assent/LAR/Witness

Protect Privacy & Maintain Confidentiality
Data Safety (6,7)
Secondary Use/Future Use

Vulnerable Populations ((3),(.111(b)))

3 Broad Criteria for IRB Approval (45 CFR 46.111 / 21 CFR 56.111)

BENEFICENCE:

- How are the risks reasonable relative to benefits?
- How are risks to subjects minimized?
- What additional safeguards for protected and vulnerable populations are in place?
- What is the safety monitoring plan to ensure subject safety and is it adequate?

JUSTICE

- How is distribution of burdens and benefits of research equitable*?

**inclusion/exclusion; not based on convenience; consider gender, age, ethnicity, SES, relevance to subject being studied, purpose of the research, research setting, vulnerabilities, etc.*

RESPECT FOR PERSONS

- How are privacy and confidentiality adequately protected?
- Is written informed consent obtained from subject/LAR (and/or does the justification for request of consent and HIPAA waiver meet specified criteria)?
- Is informed consent (or waiver justification) properly documented?

This is the floor, not the ceiling

Device Determinations

Completed by IRB Staff

For Phase 2 and 3: Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act
[USE "IS THIS A DEVICE?" CHECKLIST]

Yes. Can be excluded from "device" definition →

↓

No. Not eligible for exclusion from "device definition

↓

Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act

Yes. Eligible for Exemption

Not a “device”. 21 CFR 812 does not apply. Other regulations & policies may apply;
(IRB review may still be required)

(Exp IRB review may still be required; In Approval Letter, clarify limitations of study and why the project did not qualify as a “device” (I.e., what specific details did the study team provide, that you used, to confirm that this software function does not qualify as a “device” per the guidance)?

Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act

No. Not eligible

If determined a "device" then determine if it meets *ALL* IDE-Exemption Criteria (1-4):

1) It is non-invasive?; ***AND***

2) It does not require invasive procedure(s)?; ***AND***

3) It does not introduce energy (laser, radiation, etc.)?; ***AND***

4) The output will be confirmed by another medically established (FDA-approved) product or procedure?

Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act

No. Not eligible

IDE-Exemption Criteria (1-4):

1) It is non-invasive?; ***AND***

2) It does not require invasive procedure(s)?; ***AND***

3) It does not introduce energy (laser, radiation, etc.)?; ***AND***

4) The output will be confirmed by another medically established (FDA-approved) product or procedure?

STOP: Are you sure it meets Criteria 4? Make sure your rationale is clearly stated in the protocol

- ✓ *If an investigational test uses a* **new technology** *or* ***represents a significant technological advance****, established diagnostic products or procedures [ML, deep learning, generative AI, etc]* ***may not be adequate*** *to confirm the diagnosis provided by the investigational device.*

- ✓ *Output should not influence patient treatment or clinical management decisions* ***before the diagnosis is established by a medically established product or procedure****. Is there one?*

Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act

No. Not eligible

IDE-Exemption Criteria (1-4):
1) It is non-invasive?; ***AND***
2) It does not require invasive procedure(s)?; ***AND***
3) It does not introduce energy (laser, radiation, etc.)?; ***AND***
4) The output will be confirmed by another medically established (FDA-approved) product or procedure?

Example of device software function NOT meeting IDE-Exemption Criteria #4:

- A predictive model for pregnancy **one week after conception** is developed.
- Even though the pregnancy can be confirmed by a urine test (established procedure), in reality, **there exists no urine test that can identify pregnancy that early**.
- **Conclusion: NOT IDE-Exempt.** We cannot confirm that output until hormonal changes occur (usually 4 weeks after conception). **There is no way for us to confirm, at 1 week post conception, that the pregnancy prediction model is accurate.**

Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act

No. Not eligible

IDE-Exemption Criteria (1-4):

1) It is non-invasive?; ***AND***

2) It does not require invasive procedure(s)?; ***AND***

3) It does not introduce energy (laser, radiation, etc.)?; ***AND***

4) The output will be confirmed by another medically established (FDA-approved) product or procedure?

Yes, I confirmed it meets IDE Exempt criteria and there is documented evidence/ justification in the protocol.

IDE Exempt
(21 CFR 812.2(c))
(Risk-based design controls apply [820/809]; and IRB review required)

Assuming this is a study evaluating the performance, safety, or effectiveness of a software function…
Is that software function eligible for exclusion from the "device" definition per the Cures Act

↓

No. Not eligible

↓

IDE-Exemption Criteria (1-4):

1) It is non-invasive?; ***AND***

2) It does not require invasive procedure(s)?; ***AND***

3) It does not introduce energy (laser, radiation, etc.)?;

AND

4) The output will be confirmed by another medically established (FDA-approved) product or procedure?

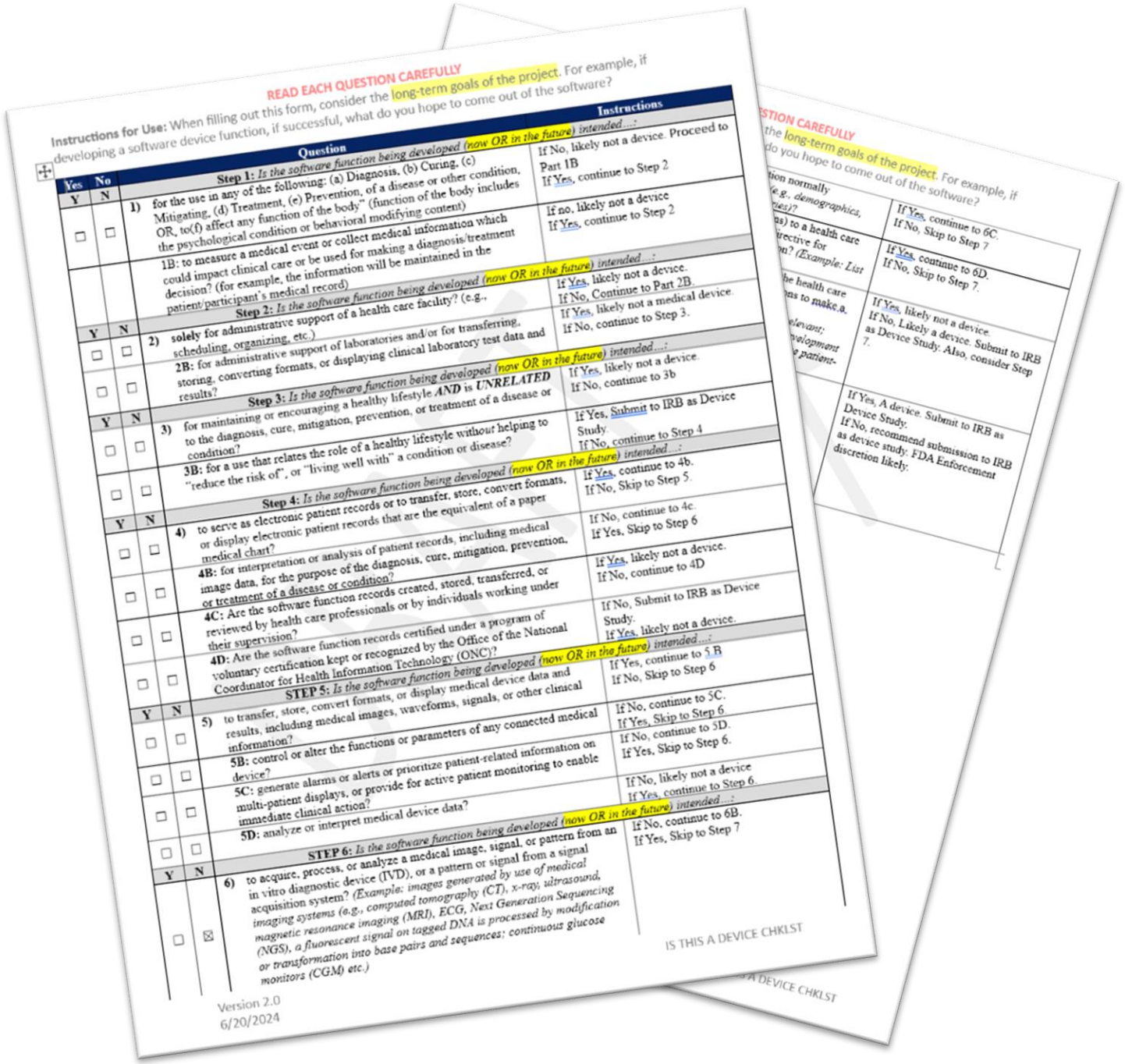
↓

At lease 1 or more of the above were not met. It does NOT Meet IDE-Exempt criteria

↓

21 CFR 812 (Significant Risk) or **812.2(b)** (Non-Significant Risk)

(IRB review required)



READ EACH QUESTION CAREFULLY

Instructions for Use: When filling out this form, consider the long-term goals of the project. For example, if developing a software device function, if successful, what do you hope to come out of the software?

Yes	No	Question	Instructions
		Step 1: *Is the software function being developed (now OR in the future) intended…:*	
☐	☐	1) for the use in any of the following: (a) Diagnosis, (b) Curing, (c) Mitigating, (d) Treatment, (e) Prevention, of a disease or other condition, OR, to(f) affect any function of the body" (function of the body includes the psychological condition or behavioral modifying content)	If No, likely not a device. Proceed to Part 1B If Yes, continue to Step 2
		1B: to measure a medical event or collect medical information which could impact clinical care or be used for making a diagnosis/treatment decision? (for example, the information will be maintained in the patient/participant's medical record)	If no, likely not a device If Yes, continue to Step 2
		Step 2: *Is the software function being developed (now OR in the future) intended…:*	
☐	☐	2) **solely** for administrative support of a health care facility? (e.g., scheduling, organizing, etc.)	If Yes, likely not a device. If No, Continue to Part 2B.
☐	☐	**2B:** for administrative support of laboratories and/or for transferring, storing, converting formats, or displaying clinical laboratory test data and results?	If Yes, likely not a medical device. If No, continue to Step 3.
		Step 3: *Is the software function being developed (now OR in the future) intended…:*	
☐	☐	3) for maintaining or encouraging a healthy lifestyle ***AND*** is ***UNRELATED*** to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition?	If Yes, likely not a device. If No, continue to 3b
☐	☐	**3B:** for a use that relates the role of a healthy lifestyle *without* helping to "reduce the risk of", or "living well with" a condition or disease?	If Yes, Submit to IRB as Device Study. If No, continue to Step 4
		Step 4: *Is the software function being developed (now OR in the future) intended…:*	
☐	☐	4) to serve as electronic patient records or to transfer, store, convert formats, or display electronic patient records that are the equivalent of a paper medical chart?	If Yes, continue to 4b. If No, Skip to Step 5.
☐	☐	**4B:** for interpretation or analysis of patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition?	If No, continue to 4c. If Yes, Skip to Step 6
☐	☐	**4C:** Are the software function records created, stored, transferred, or reviewed by health care professionals or by individuals working under their supervision?	If Yes, likely not a device. If No, continue to 4D
☐	☐	**4D:** Are the software function records certified under a program of voluntary certification kept or recognized by the Office of the National Coordinator for Health Information Technology (ONC)?	If No, Submit to IRB as Device Study. If Yes, likely not a device.
		STEP 5: *Is the software function being developed (now OR in the future) intended…:*	
☐	☐	5) to transfer, store, convert formats, or display medical device data and results, including medical images, waveforms, signals, or other clinical information?	If Yes, continue to 5.B If No, Skip to Step 6
☐	☐	**5B:** control or alter the functions or parameters of any connected medical device?	If No, continue to 5C. If Yes, Skip to Step 6
☐	☐	**5C:** generate alarms or alerts or prioritize patient-related information on multi-patient displays, or provide for active patient monitoring to enable immediate clinical action?	If No, continue to 5D. If Yes, Skip to Step 6.
☐	☐	**5D:** analyze or interpret medical device data?	If No, likely not a device If Yes, continue to Step 6.
		STEP 6: *Is the software function being developed (now OR in the future) intended…:*	
☐	☒	6) to acquire, process, or analyze a medical image, signal, or pattern from an in vitro diagnostic device (IVD), or a pattern or signal from a signal acquisition system? *(Example: images generated by use of medical imaging systems (e.g., computed tomography (CT), x-ray), ultrasound, magnetic resonance imaging (MRI), ECG, Next Generation Sequencing (NGS), a fluorescent signal on tagged DNA is processed by modification or transformation into base pairs and sequences; continuous glucose monitors (CGM) etc.)*	If No, continue to 6B. If Yes, Skip to Step 7

IS THIS A DEVICE CHKLST

Version 2.0
6/20/2024

Is My Clinical Decision Support Tool a "Medical Device"?

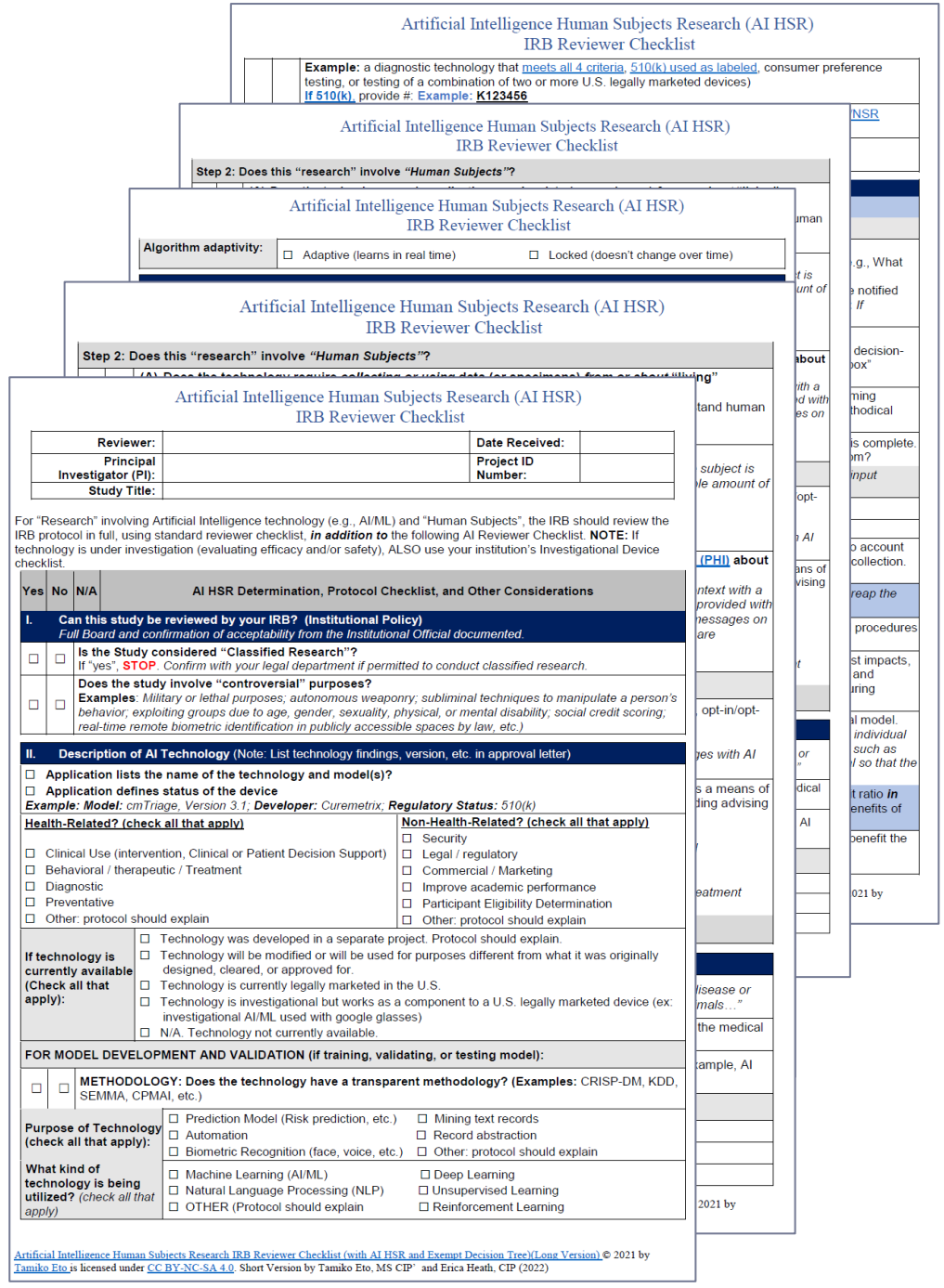
There's a CHECKLIST for that!

Eto.Tamiko@mayo.edu

IRB & HRPP Checklists...

- Visit here to access the most recent/updated:
  - AI HSR IRB Reviewer Checklist
  - AI HSR Exempt Determination Decision Tree
  - AI HSR Human Subjects Research Decision Tree

- Learn how to use the AI HSR Checklist here (must be a PRIM&R member):



Artificial Intelligence Human Subjects Research (AI HSR)
IRB Reviewer Checklist

Reviewer:	Date Received:
Principal Investigator (PI):	Project ID Number:
Study Title:	

For "Research" involving Artificial Intelligence technology (e.g., AI/ML) and "Human Subjects", the IRB should review the IRB protocol in full, using standard reviewer checklist, ***in addition to*** the following AI Reviewer Checklist. **NOTE:** If technology is under investigation (evaluating efficacy and/or safety), ALSO use your institution's Investigational Device checklist.

Yes	No	N/A	AI HSR Determination, Protocol Checklist, and Other Considerations
			I. Can this study be reviewed by your IRB? (Institutional Policy) *Full Board and confirmation of acceptability from the Institutional Official documented.*
☐	☐		**Is the Study considered "Classified Research"?** If "yes", **STOP**. *Confirm with your legal department if permitted to conduct classified research.*
☐	☐		**Does the study involve "controversial" purposes?** **Examples**: *Military or lethal purposes; autonomous weaponry; subliminal techniques to manipulate a person's behavior; exploiting groups due to age, gender, sexuality, physical, or mental disability; social credit scoring; real-time remote biometric identification in publicly accessible spaces by law, etc.)*
			II. Description of AI Technology (Note: List technology findings, version, etc. in approval letter)
			☐ **Application lists the name of the technology and model(s)?** ☐ **Application defines status of the device** ***Example: Model:*** *cmTriage, Version 3.1;* ***Developer:*** *Curemetrix;* ***Regulatory Status:*** *510(k)*

Health-Related? (check all that apply)	Non-Health-Related? (check all that apply)
☐ Clinical Use (intervention, Clinical or Patient Decision Support)	☐ Security
☐ Behavioral / therapeutic / Treatment	☐ Legal / regulatory
☐ Diagnostic	☐ Commercial / Marketing
☐ Preventative	☐ Improve academic performance
☐ Other: protocol should explain	☐ Participant Eligibility Determination
	☐ Other: protocol should explain

If technology is currently available (Check all that apply):	☐ Technology was developed in a separate project. Protocol should explain. ☐ Technology will be modified or will be used for purposes different from what it was originally designed, cleared, or approved for. ☐ Technology is currently legally marketed in the U.S. ☐ Technology is investigational but works as a component to a U.S. legally marketed device (ex: investigational AI/ML used with google glasses) ☐ N/A. Technology not currently available.

FOR MODEL DEVELOPMENT AND VALIDATION (if training, validating, or testing model):

☐ ☐ **METHODOLOGY: Does the technology have a transparent methodology? (Examples:** CRISP-DM, KDD, SEMMA, CPMAI, etc.)

Purpose of Technology (check all that apply):	☐ Prediction Model (Risk prediction, etc.) ☐ Automation ☐ Biometric Recognition (face, voice, etc.)	☐ Mining text records ☐ Record abstraction ☐ Other: protocol should explain
What kind of technology is being utilized? *(check all that apply)*	☐ Machine Learning (AI/ML) ☐ Natural Language Processing (NLP) ☐ OTHER (Protocol should explain	☐ Deep Learning ☐ Unsupervised Learning ☐ Reinforcement Learning