

**Guidance on Use of Investigational Medical Devices in Human Subjects Research**

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## Device Definitions:

### 1) What is a Medical Device?

A [medical device](#) is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man,  
OR
- intended to affect the structure or any function of the body of man,  
AND which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

This may include AI, machine learning, clinical decision support software, invitro diagnostic testing, and traditional medical devices, etc.

### 2) What is an Investigation?

A [clinical study](#) means research according to a protocol involving one or more human subjects to evaluate biomedical or health-related outcomes, including interventional studies and observational studies.

A [clinical investigation](#) or research involving one or more subjects *to determine the safety or effectiveness of a device* when the test article is FDA-regulated. De-identified data and specimen fall under human research when used in a clinical investigation.

A [clinical trial](#) is a research study where human subjects are prospectively assigned to one or more interventions to *evaluate the effects of those interventions* on the safety and effectiveness of a new drug, biological product, or medical device. This is a specific type of clinical investigation.

### 3) What is an Investigational Medical Device?

An [investigational device](#) means a device, including a transitional device that is the object of an investigation.

Simply using a device as part of a study does not make the device investigational. For example, if a non-invasive, unapproved device is used to make measurements as part of a study, but the study is not about the device, then the device is not an investigational device for the purposes of that study.

In another example, if an investigator wishes to use an unapproved medical device to measure cerebral blood flow but the study is not about the device (not assessing the safety or effectiveness of the device), then for that study, the unapproved device would not be investigational. Whereas the device would be an investigational medical device when used in a study designed to assess the feasibility and safety of making cerebral blood flow measurements during cardiac surgery.

The following steps address assessing when and which FDA regulations apply for studies using an investigational medical device.

## Assessing the Application of FDA Regulations:

### 4) When do the FDA regulations apply?

FDA regulations apply when a study evaluates the safety or effectiveness of an investigational medical device in subjects, healthy control subjects, or human specimens. FDA Informed Consent (21 CFR 50) and IRB (21 CFR 56) regulations apply as well.

### 5) When do the FDA regulations not apply?

FDA regulations would generally not apply to studies:

- using an FDA approved device to test a physiologic principle where no data is collected about the device;
- using an FDA approved device to address a research question and no data is collected about the device; or
- using an FDA approved device for clinical purposes (e.g., monitor a side effect, measure treatment progress as long as there is no intent to collect safety or effectiveness data or develop the device for marketing).

An example would be use of magnetic resonance imaging (MRI) to measure a clinical outcome in a study that has nothing to do with the MRI itself.

However, if the device used for one of these purposes is homemade by the investigator, (e.g., a lever designed to raise the arm to measure flexibility), the informed consent should state that the device is **not approved by the FDA**.

6) What is an Investigational Device Exemption (IDE) and when is it required?

An IDE (issued by the FDA) allows the investigational device to be used in a clinical investigation in order to collect safety and efficacy data required to support a marketing application. The term “exemption in this case” means exempt from laws prohibiting unapproved products to move in interstate commerce.

FDA Investigational Device Exemptions (IDE) (21 CFR 812) regulations may apply for studies designed to:

- support marketing applications;
- collect safety and effectiveness information (e.g. for a new intended use of a legally marketed device);  
and
- Studies of an unapproved device or a new intended use of an approved device, even if no marketing application is planned.

### **7) What are the three regulatory categories for device studies described in the IDE regulations (21 CFR 812)?**

Research that involves assessing the safety or effectiveness of a medical device must fit in ONE of the following categories:

1. Significant Risk (SR)-device research with formal IDE submission to FDA;
2. Non-Significant Risk (NSR) device research, which with IRB approval is considered to have an approved IDE; referred to as an Abbreviated IDE;
3. Studies exempt from IDE requirements (see #11, below)

Significant risk and non-significant risk device determinations are sent to the IRB panel.

[Use WORKSHEET: Devices \(HRP-307\)](#) in order to help decide whether an investigational device requires an investigational device exemption (IDE), qualifies for an abbreviated IDE or is IDE exempt.

***See Appendix, Flowchart 1: IDE Determinations***

### **8) Who decides whether a device study is SR or NSR?**

Sponsors are responsible for making the initial risk determination and presenting it to the IRB. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. If the IRB disagrees with the Sponsor's NSR determination, the PI may be asked to contact the FDA to obtain an IDE.

If FDA has already made the SR or NSR determination for the study, the agency's determination is final.

**9) What are the IRB's responsibilities when it receives a device study for IRB review?**

• If the device, as used in the study, is NOT IDE exempt and the study does NOT have a valid IDE or FDA correspondence stating the device is NSR, then the IRB makes the SR or NSR determination **based on the proposed use of the device in the study**. The SR/NSR determination is made by the **full IRB at a convened meeting** using information such as the sponsor's risk designation and justification criteria, a description of the device, reports of prior investigations, proposed investigational plan, and subject selection criteria. The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination.

- An IRB may agree or disagree with the sponsor's initial NSR assessment.
- If the IRB determines the study is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to FDA.
- If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must tell the clinical investigator, and where appropriate, the sponsor. (See 21 CFR 812.66)
- An IRB may approve the study as an SR device study, but the study may not begin until FDA approves the sponsor's IDE application (or gives conditional approval).
- To facilitate the IRB's review of the study, an IRB may ask the sponsor for proof (i.e., a copy of FDA's approval or conditional approval letter) that an SR study has an FDA-approved IDE application.
- The IRB should document its SR/NSR determination in the IRB meeting minutes.

***See Appendix, Flowchart 2: Use of Device Decision Tree***

**10) What should the IRB Panel consider when making the SR and NSR determination?**

The risk determination is based on the proposed use of a device in an investigation, and not on the device alone.

SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject.

The IRB Panel should consider the potential harm the procedure could cause as well as the potential harm caused by the device.

[Use CHECKLIST: Non-Significant Risk Device \(HRP-418\)](#) to determine if the device study is SR or NSR.

### 11) What is meant by IDE Exempt?

Certain device studies are "[Exempt](#)" from the IDE requirements. Exempted investigations include investigations involving one of the following:

1. The most common IDE exempt studies are those involving a marketed medical device in which the device is used or investigated in accordance with the indications in the cleared labeling. For these studies the investigator should provide, and the IRB should review, label information in order to compare the intended use in the protocol with the approved indications. Device approval indications may also be found by searching one of the FDA Device [Approvals and Clearances databases](#).
2. Other examples of studies exempt from IDE requirements are consumer preference testing, testing of a device modification or testing of a combination of two or more devices in commercial distribution if the testing does NOT collect safety or effectiveness data, or put subjects at additional risk.
3. In addition, [diagnostic device studies](#) [e.g., **in-vitro diagnostic reagents and test kits such as pregnancy test kits, imaging systems such as magnetic resonance imaging (MRI), machine learning and artificial intelligence (AI) models that utilize patient data to generate predictive outcomes**] are exempt from the IDE requirements under certain circumstances. A study meets IDE exempt category 2, as long as:
  - the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing:
    - (i) is noninvasive;
    - (ii) does not require an invasive sampling procedure that presents significant risk;
    - (iii) does not by design or intention introduce energy into a subject; and
    - (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.[21 CFR 812.2(c)(3)].

**See Appendix, Flowchart 3: AI as SaMD Determinations**

## 12) Does device classification (Class I, II, III) factor into IRB determinations?

A sponsor's detailed protocol may list a device as [Class I, II or III](#). FDA classifies devices based on the level of control necessary to assure the safety and effectiveness of the device for marketing (**not research**). Controls range from general requirements such as labeling, not misbranding, and good manufacturing practices to special controls such as specific instructions for use or post-marketing surveillance requirements.

The classification is risk-based and is indicative of the type of submission required for the FDA to clear a device for marketing. Class II and Class III devices require the type of marketing route that most often involves clinical trials. Therefore, these are the types of devices seen in research for which the IRB is involved in the regulatory determinations addressed in the questions above.

Simply claiming that a device is Class I or II isn't enough to determine it's a non-significant risk (NSR) device. To qualify as an FDA-approved, IDE exempt Category 1 device, it must either be officially registered and listed in the FDA's device registry or have a 510(k) clearance letter issued by the FDA. The device must be used as labeled by the 510k letter.

## 13) When can an investigational device study be eligible for Expedited IRB review?

For a device study to be eligible for Expedited Review under Expedited Category 1b (*not to be confused with IDE exempt category #1*), **the device must present no more than minimal risk to the subject, and meet one of the criteria in Category 1b:**

**Expedited Category 1b-** Research on medical devices for which

- (i) an IDE application (21 CFR Part 812) is not required\*<sup>\*</sup>; or
- (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling\*\*<sup>\*\*</sup>.

*\*Example of (i): Study presents documentation from FDA indicating that an IDE application is not required, or study meets all criteria to be IDE exempt in vitro diagnostic device, including AI/ML software used in diagnosis, 21 CFR 812.2(c)(3).*

*\*\* An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements- 21 CFR 812.2(c)(1 or 2).*

**Note:** *Expedited Category 1b can be used if the device is being tested as labeled or if it's a diagnostic device and the study is minimal risk. In this case, the study will be FDA regulated.*

*Expedited Category 1b should not be used for studies involving only the use of a device (without testing or data collection on or about the device).*

*Expedited Category 4 (collection of data through noninvasive procedures routinely employed in clinical practice) should be considered for studies that **use, but not test**, a device.*

*Examples:*

- *A study obtaining ultrasounds from participants for research purposes would fall under expedited category 4.*
- *A study evaluating the efficacy of an ultrasound device to diagnose a condition, as it is labeled for by the FDA, would likely fall under expedited category 1b.*

## **Device Subsets:**

### **14) What if I am using a Mobile Application in my research study?**

The [FDA mobile medical device regulations](#) apply if you are using a mobile application in a research study, and that is being used to facilitate the diagnosis, or mitigation, of a disease, or affect the function or structure of the human body.

Please use the [Guidance for Research Involving Mobile Apps or Mobile Medical Apps](#) and refer to [WORKSHEET: Mobile Apps and Mobile Medical Apps \(HRP-336\)](#) if the study uses Mobile Apps in addition to the device regulations to determine if the mobile application medical device is NSR.

### **15) What is a Humanitarian Use Device (HUD)?**

A HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

Use of a HUD in medical practice, within its approved labeling does not constitute research. Initial IRB approval of a HUD should be performed at a convened IRB meeting.

Humanitarian Device Exemption (HDE) holder may collect safety and effectiveness data in a clinical investigation for the HDE-approved indication(s) without an IDE.

Clinical investigation of HUD for different indication must be conducted in compliance with IDE regulations.

[Use WORKSHEET: Criteria for Approval for HUD \(HRP-323\)](#)

## 16) What is Software as a Medical Device (SaMD)?

SaMD is software that is intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device. Examples include software that drives an infusion pump, image processing for cancer detection, and software that regulates a pacemaker

Clinical decision support (CDS) is a subset of SaMD. It is a software function that provides health care professionals and patients with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care.

To determine if software meets the definition of a medical device, the primary consideration should be whether the software is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, per the FDA's definition of a medical device.

Not all clinical decision support software used in healthcare settings are medical devices and therefore subject to FDA oversight as a device.

***See Appendix, Table 1: CDS vs. SaMD for a comparison of what is considered a medical device and what is considered non-device CDS.***

For CDS software functions to be excluded from the definition of a medical device, the software must meet ALL 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 AND
- (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.

***See Appendix, Flowchart 4: Clinical Decision Support Tools***

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**17) Other Helpful Links and Resources:**

[Frequently Asked Questions About Medical Devices | FDA](#)

[Significant Risk and Nonsignificant Risk Medical Device Studies | FDA](#)

[FAQs about Investigational Device Exemption | FDA](#)

[In Vitro Diagnostic \(IVD\) Device Studies - Frequently Asked Questions | FDA](#)

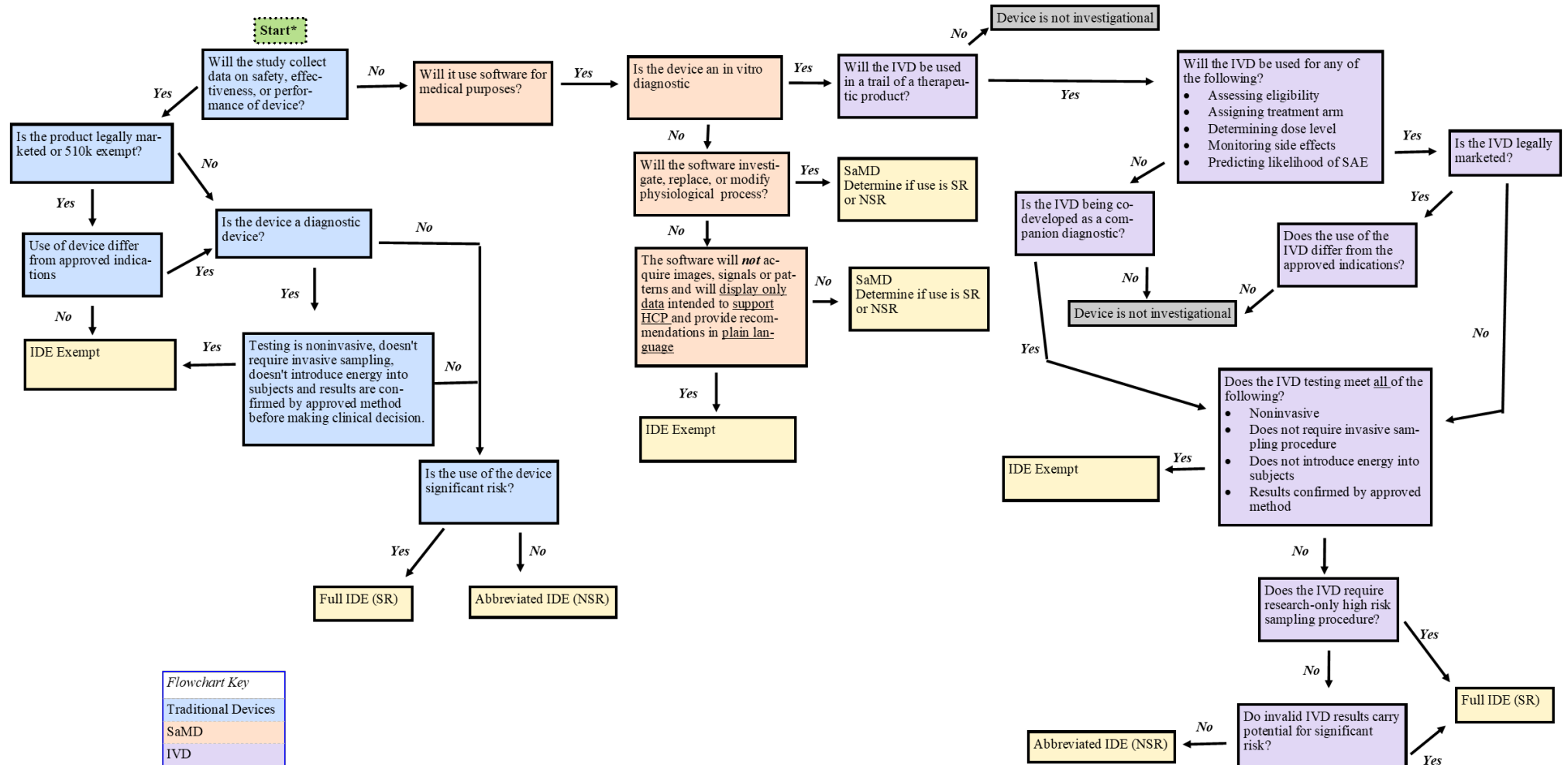
[Examples of Software Functions That Are NOT Medical Devices | FDA](#)

[Humanitarian Device Exemption \(HDE\) Program | FDA](#)

[General Wellness: Policy for Low Risk Devices | FDA](#)

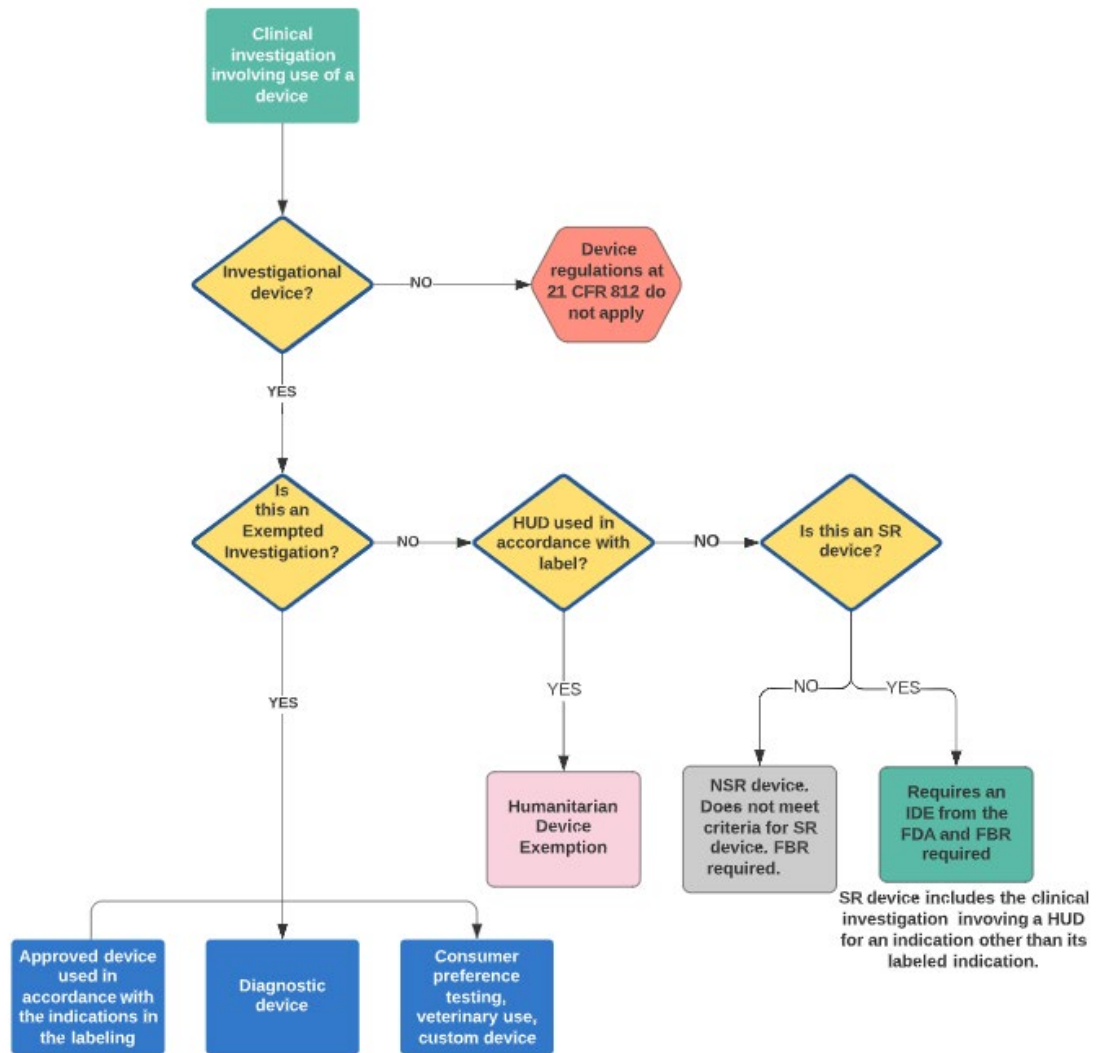
[Software as a Medical Device \(SaMD\) | FDA](#)

18) Appendix of Device Flowcharts and Tables:

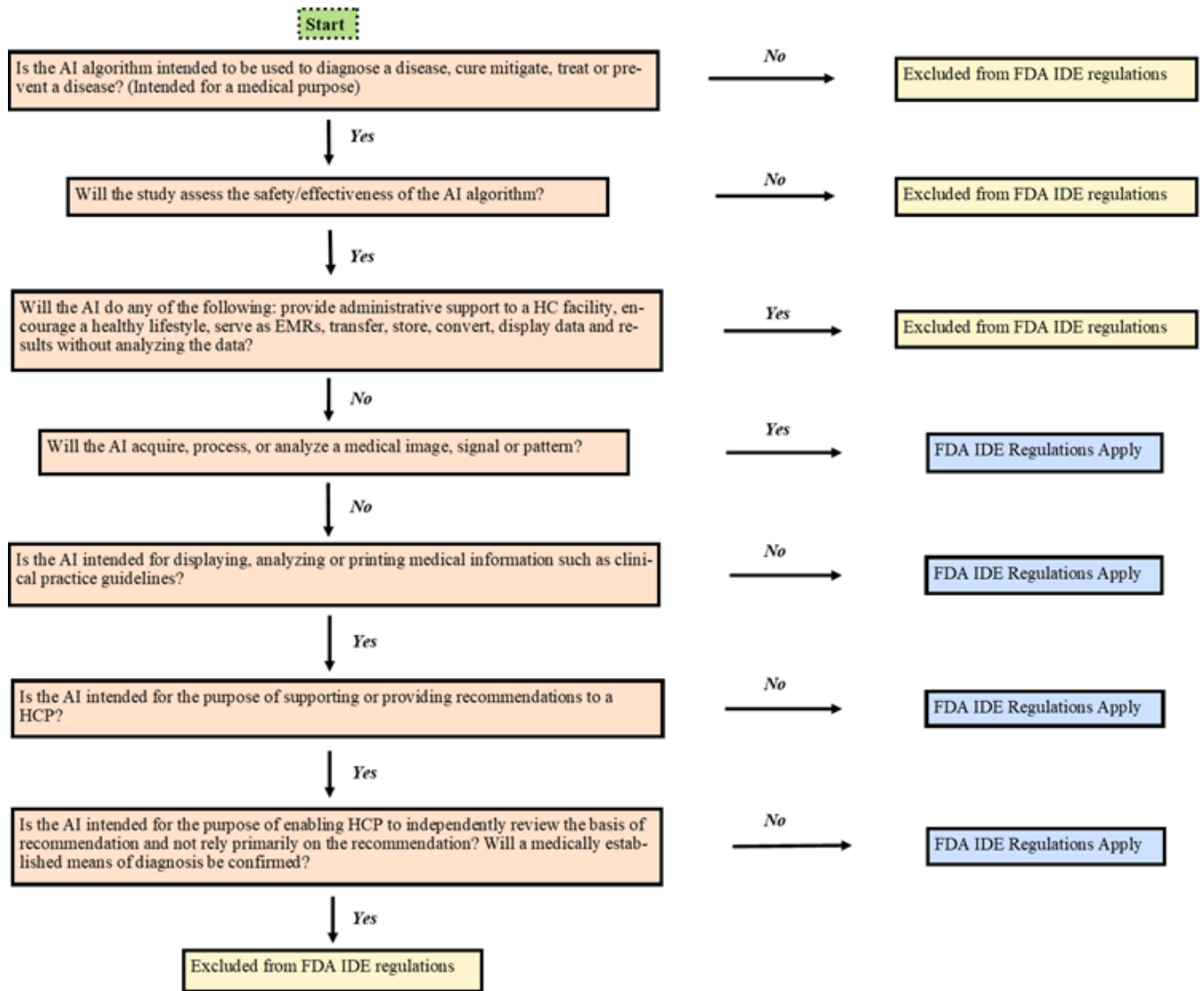


Flowchart 1 – IDE Determinations: The purpose of this flowchart is to help IRB analysts, panel members, and researchers determine whether the device falls under FDA regulations as an investigational device.

\*Note that the evaluation of the device is being done prospectively in all scenarios through a clinical investigation.



Flowchart 2 – Use of Device Decision Tree: The purpose of this flowchart is to help IRB analysts, panel members, and researchers determine whether the use of a device is considered investigational under FDA regulations.



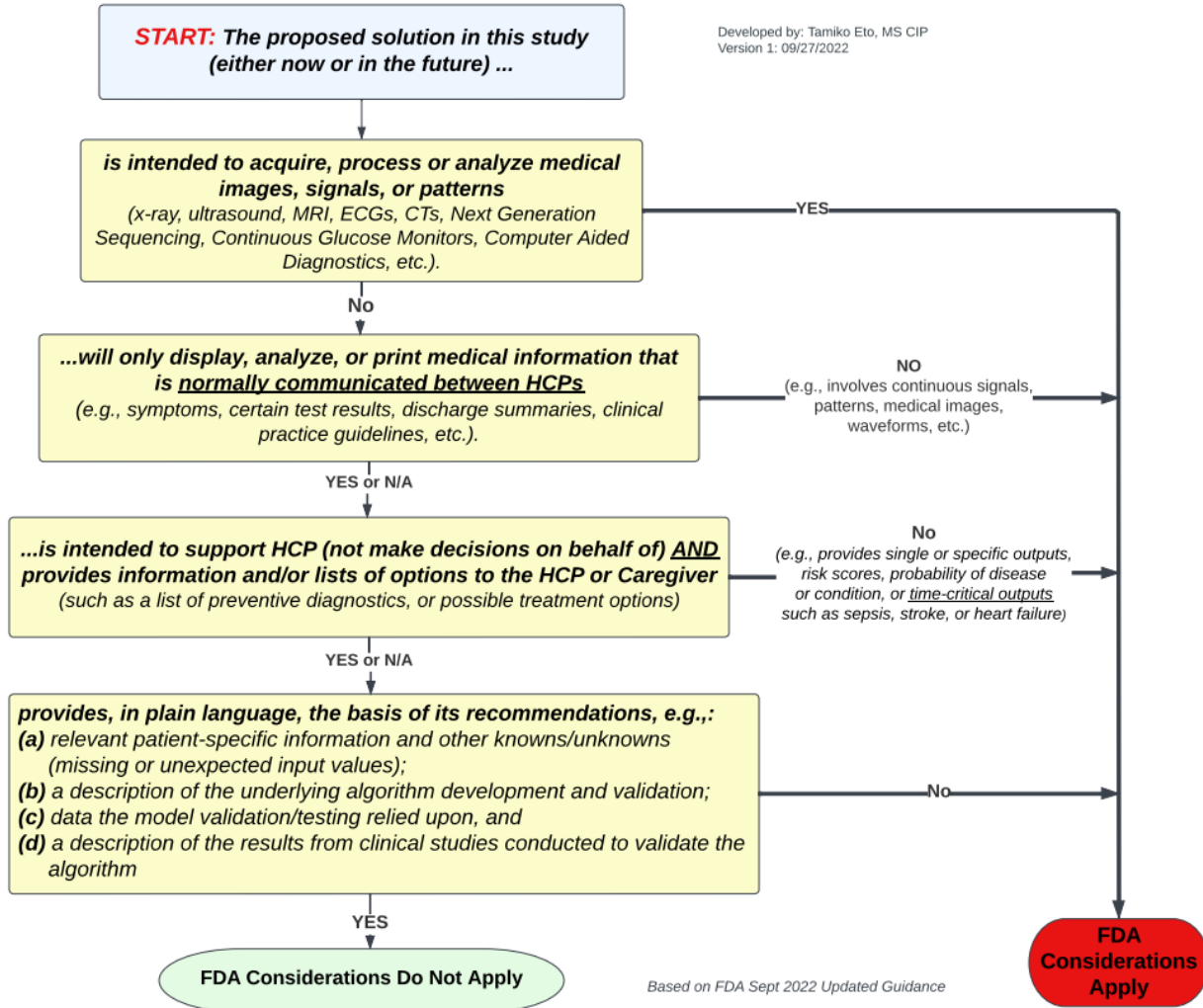
Flowchart 3 – AI as SaMD Determinations: The purpose of this flowchart is to help IRB analysts and researchers determine whether an AI algorithm falls under FDA regulations as an investigational device.

## CDS vs. SaMD

Software does not acquire process, analyze medical images, signals, or patterns	Software <b>acquires, processes, or analyzes</b> images/data. Examples include in vitro diagnostics, MRI, glucose monitoring, computer aided detection/diagnostics
Software function displays, analyzes, or prints medical information communicated between healthcare professionals. Examples include: EMRs, reports from a study, and information whose relevance to clinical decision is understood	Software displays, analyzes, or prints images specific to participant that have <b>possible clinical relevance to diagnosis and treatment decisions</b> , such as medical images, ECGs, and continuous signals/patterns (blood pressure monitor)
Software function provides recommendations (information/options) rather than a specific output or directive, such as a report of common treatment options for a diseases or condition in a search engine	Software <b>provides specific outputs or directives based on patient inputs</b> , such as patient risk scores for a disease/condition or patient's probability of a disease or condition, and time critical outputs for clinical decision making.
Software function provides the basis of the recommendations so that the healthcare provider does not rely primarily on any recommendations to <u>make a decision</u> , such as plain language descriptions of software purpose, medical input, or relevant patient-specific information	Software provides <b>output without basis of recommendations and to be <u>primarily</u> relied upon in decision making</b> , such as a singular response upon which the physician relies on for <u>making a decision</u> in diagnosis, treatment, or mitigation.

Table 1 – CDS vs. SaMD: The purpose of this table is to provide IRB analysts and researchers with a comparison of what is considered software as medical device and what is considered non-device clinical decision support software.

CLINICAL DECISION SUPPORT TOOLS: WHEN DO FDA REGULATIONS APPLY?



Flowchart 4 – Clinical Decision Support Tools: The purpose of this flowchart is to help IRB analysts and researchers determine whether a clinical decision support tool is subject to FDA regulations.