Mass General Brigham

Guidance for Deploying Medical Image-based Software – including Algorithms – in the Clinical Setting

Purpose: Software that satisfies the definition of a "medical device" under FDA regulations is subject to the same FDA regulatory oversight as any other medical device. This guidance document provides information regarding FDA requirements when investigating medical image-based software in clinical research. In most circumstances, such deployment activities should be conducted according to the FDA Investigational Device Exemption ("IDE") regulations set forth in 21 CFR Part 812, as administered by the Institutional Review Board ("IRB").

A. Definitions

1. **Deployment Plan:** The methods describing the proposed use of the medical device, what is being studied, monitored, tested, validated, etc., as part of the path to full clinical deployment. This Deployment Plan is included in the Protocol Summary of the submitted IRB application.

2. **Investigational Software:** For the purposes of this document, software (including algorithms) is considered investigational software when it is the object of research involving subjects (including use of identified or de-identified data) to determine its effectiveness or safety. This includes newly developed software, or software that is derived from or a modification of existing software, or software that is being evaluated in a study even if it has received FDA premarket approval (PMA) or clearance (510(k)).

3. **Medical Image:** A visual representation of the interior (e.g. organs, tissues) or exterior of the body (e.g. skin) created for the purposes of clinical diagnosis, analysis, medical intervention, and/or treatment; including, but not limited to, radiological imaging techniques, photographs, etc.

4. **Medical Device:** For the purposes of this guidance and in most circumstances, software will meet the FDA definition of a medical device if the software is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease". Please note, **software intended to acquire, process, or analyze a medical image** or signal from a signal acquisition system currently **is considered a medical device by the FDA.** Most clinical decision support tools used in a research study are considered regulated medical devices with very few exceptions. Software that meets the FDA definition of a medical device is regulated in the same manner as other medical devices.

B. Proposed Use of the Medical Device

Clinical Deployment

When the software or algorithm has been trained, tested, validated and all additional research related to the safety or efficacy is complete, it may be approved by the appropriate clinical leadership and governing body for operational use in the clinical workflow. Under this approval, only continuous real-world monitoring and related improvements in the device, software or tool may be conducted without an IRB. Any new or additional investigational or other research use must be reviewed by the IRB.

Clinical Investigation

In most situations, deploying software or an algorithm in a clinical setting will be part of a clinical investigation studying the safety and effectiveness of the algorithm. Examples include but are not limited to: comparing the software and its algorithm to standard of care, studying the impact of the algorithm on consistency of diagnosis, or studying the impact of the algorithm on workflow.

> *It is very rare that software or algorithms developed for clinical use would be considered a tool to measure or collect data or study human physiology. For example, consider an algorithm for automatic segmentation used to measure the size of a tumor: if the size of the tumor is being collected, it potentially may be considered a tool if the algorithm has been previously established clinically or scientifically as a valid method/tool; however, if the accuracy of the measurement or segmentation is being studied, the algorithm would not be considered a tool and the process would instead be considered that of investigation of a medical device.*

C. Determining Need for an IDE under FDA Regulations

Overview

All clinical research of investigational software must be reviewed by the IRB and must have an approved IDE or be exempt from the FDA's IDE regulations. The purpose of the IDE is to allow the investigational software to be used in a clinical study to collect efficacy and safety data. The IRB may determine that the use of an investigational device in the context of a research study is either exempt from needing an IDE, meets the definition of a Non-Significant Risk device, or that it requires an IDE to be conducted.

1. Exempt from IDE:

The following types of studies using investigational software may be determined by the IRB to be exempt:

- Studies using FDA approved or cleared software in accordance with FDA approved labeling;
- Studies using software only as a diagnostic device if it complies with the labeling requirements in §809.10(c) 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 by another medically established diagnostic product or procedure; and
- Studies using the software only in the context of user preference testing and in the absence of any other aims (e.g., clinician preference for a display is being studied; accuracy or comparison to standard of care is not part of the study).

The IRB is responsible for determining whether the study meets any of the criteria listed above. When relying on the "diagnostic use" exception, investigators are urged to include a description in the Protocol Summary of how "confirmation by another medically established diagnostic product or procedure" is incorporated into the deployment plan. Examples may include: (i) a description of an algorithm used in evaluation or "shadow mode," (i.e., with diagnosis being made only by standard clinical pathways); or (ii) a description of how the radiologist is reminded to use his/her independent clinical judgement (i.e. the radiologist may choose whether or not to utilize an algorithm available in the clinical workflow or "production mode"). Investigators should also provide any supporting documentation demonstrating that their department/division does not deploy such software without human oversight, if applicable.

2. *Significant Risk (SR) vs. Non-Significant Risk (NSR) Device Determination*

If the investigational use of the software does not meet the exempt criteria, a determination must be made whether the device study presents a "Significant Risk" (SR) or a "Non-Significant Risk" (NSR). The judgement about whether a study poses a significant risk is based on the significance of the potential harm that may result from participation in the study, including the use of the device, and is determined by the FDA and/or the IRB. *(see FDA Guidance)*

Significant Risk Device Study Criteria:

Criteria 1	Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
Criteria 2	Purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
Criteria 3	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.
Criteria 4	Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the investigator is pursuing an NSR determination by the IRB, the Protocol Summary must clearly describe the protocol specific reasoning as to why the potential for serious risk to the health, safety, or welfare of a subject is not present.

a. *Examples:*

- Criterion 2 may apply if the algorithm is automatically making changes to a machine supporting or sustaining human life or if the algorithm is making life-supporting or life-sustaining treatment or intervention recommendations to the care provider. The deployment plan should document how human medical expertise and standard clinical judgement is the primary decision-making method to reduce the risk to the health, safety, or welfare of a subject.
- Criterion 3 may apply for algorithms aiming to improve diagnoses, treatments, or otherwise improve human health; deployment plans should detail how potential risks to the health, safety, or welfare of a subject will be mitigated. Other considerations include the seriousness of the condition being studied, the level of automation and the degree of human oversight.

b. *Potential Outcomes:*

- If none of the Significant Risk Device Study criteria are met, the IRB may be able to make the NSR determination. If the IRB finds the study is NSR, the device is considered to have an Abbreviated IDE (21 CFR 812.2(b)), the investigation may proceed without FDA approval after the IRB approves the study.
- If the IRB is unable to determine that a study is Significant Risk or if the IRB determines the study is Significant Risk, the PI will be required to query the FDA and/or submit an IDE application to FDA.

Please note, the FDA has the ultimate decision in determining if a device is SR or NSR. On some occasions, FDA may overrule the IRB's decision that a device presents NSR or SR. When FDA overrules an IRB's NSR determination, an IDE application must be submitted to FDA. On the other hand, when FDA considers the device to be NSR, FDA may return an IDE application to the investigator or sponsor.

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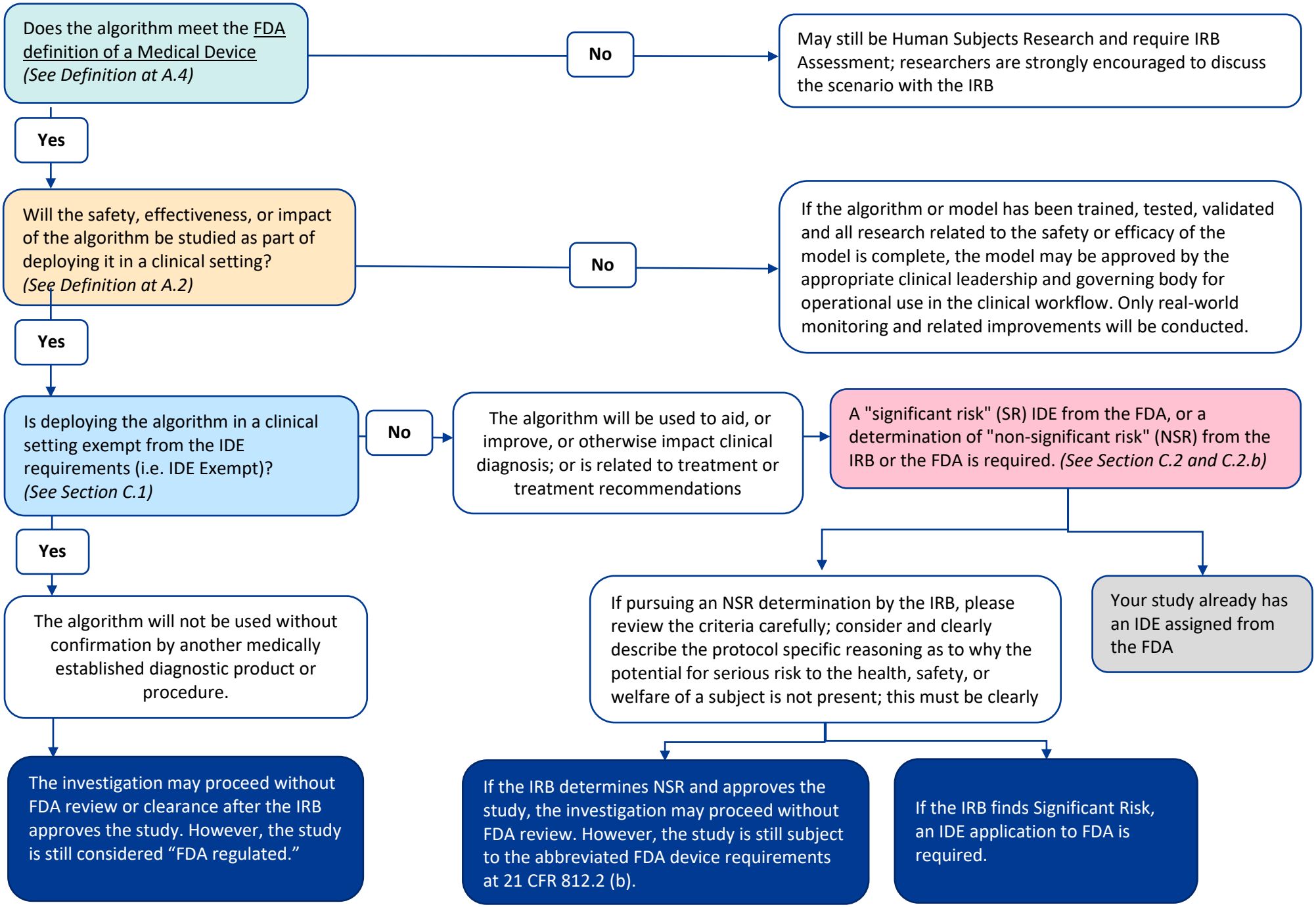
Attachment 1

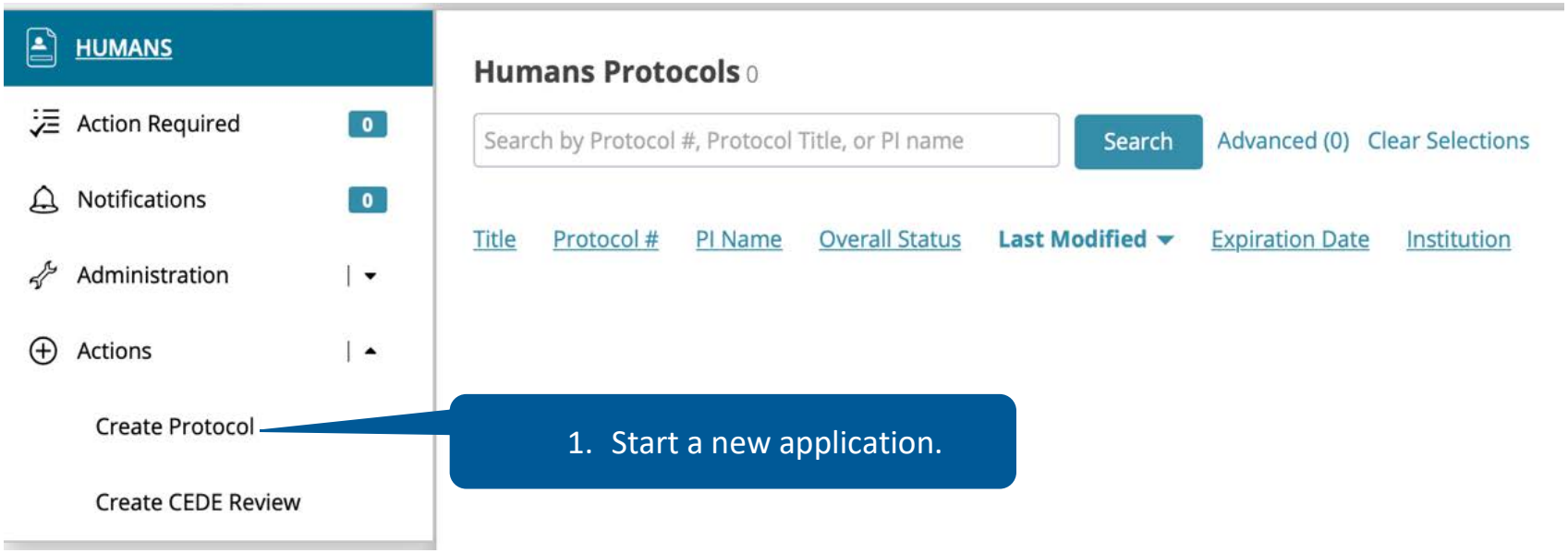


Attachment 2

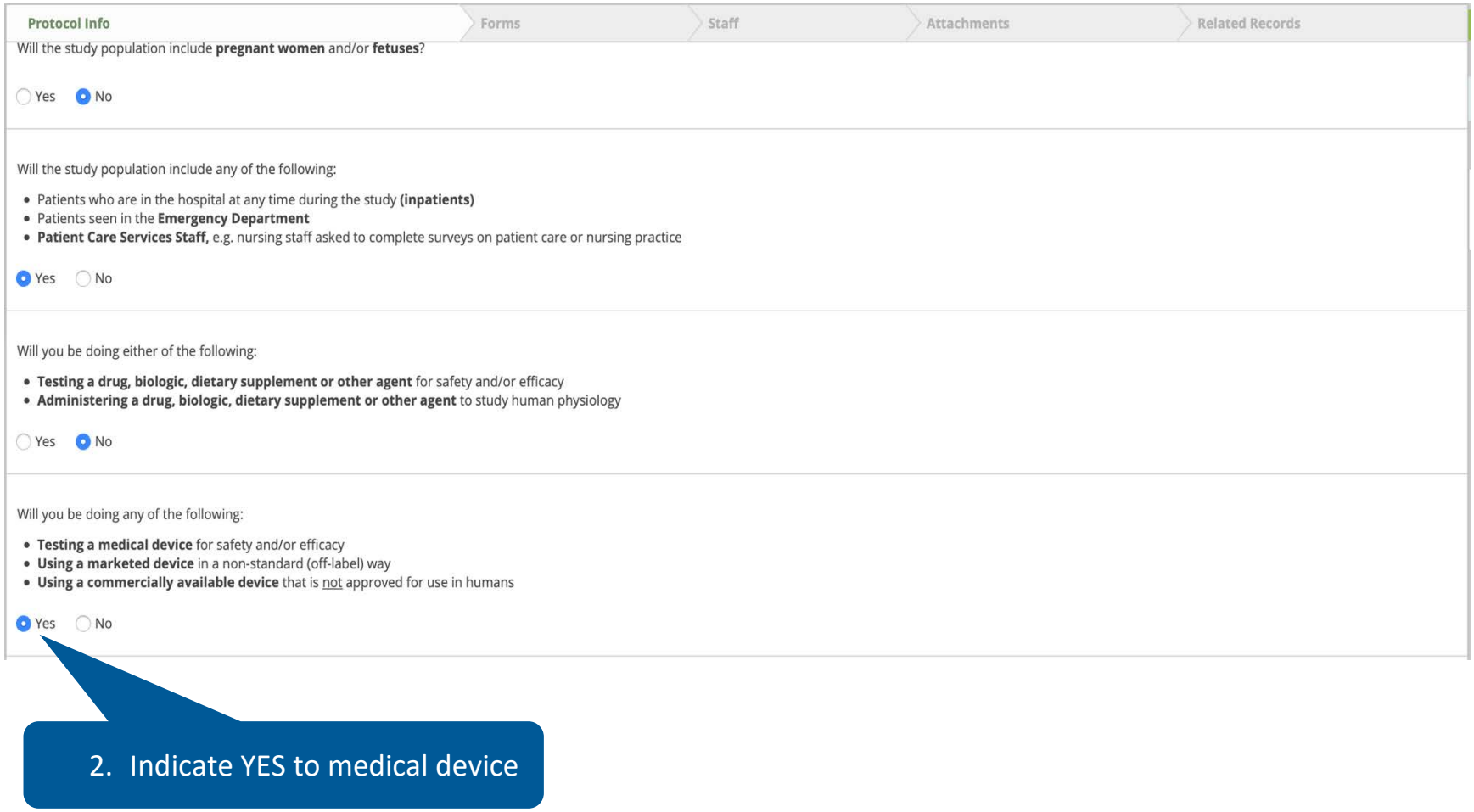
Please follow the directions below for completing the MGB IRB application in Insight for your protocol.

Step 1: Process to Initiate IRB Application: All AI software applications complete this part.

1. Start a new application in Insight by choosing to “Create Protocol” on the left-side navigation menu

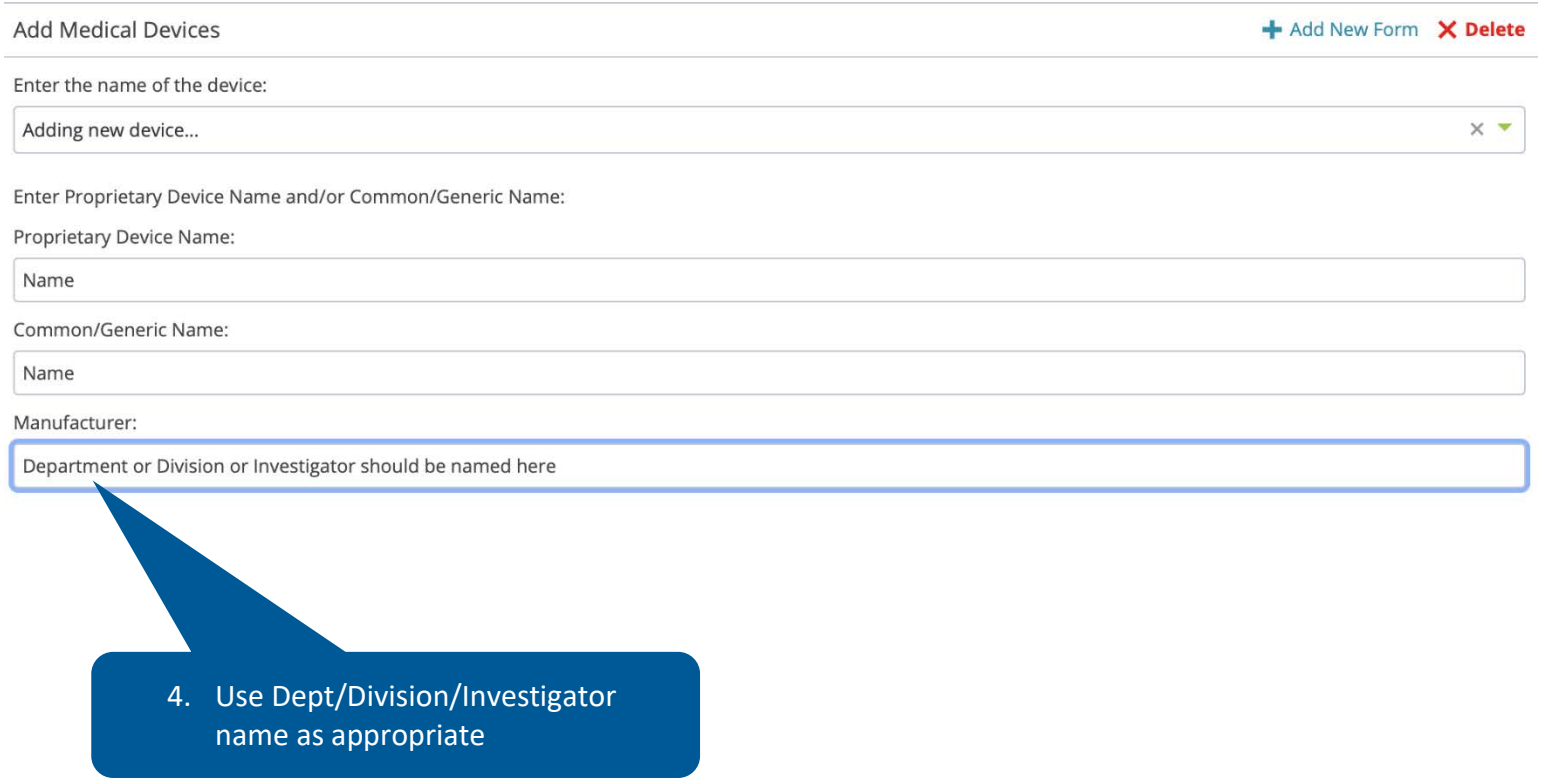


2. Indicate YES to indicate you will be “Testing a medical device for safety and/or efficacy”



3. After completing the Protocol Information and clicking “Create Protocol” (right navigation pane in Insight), complete the forms including the Medical Device form. To complete the Medical Device form, follow directions below.

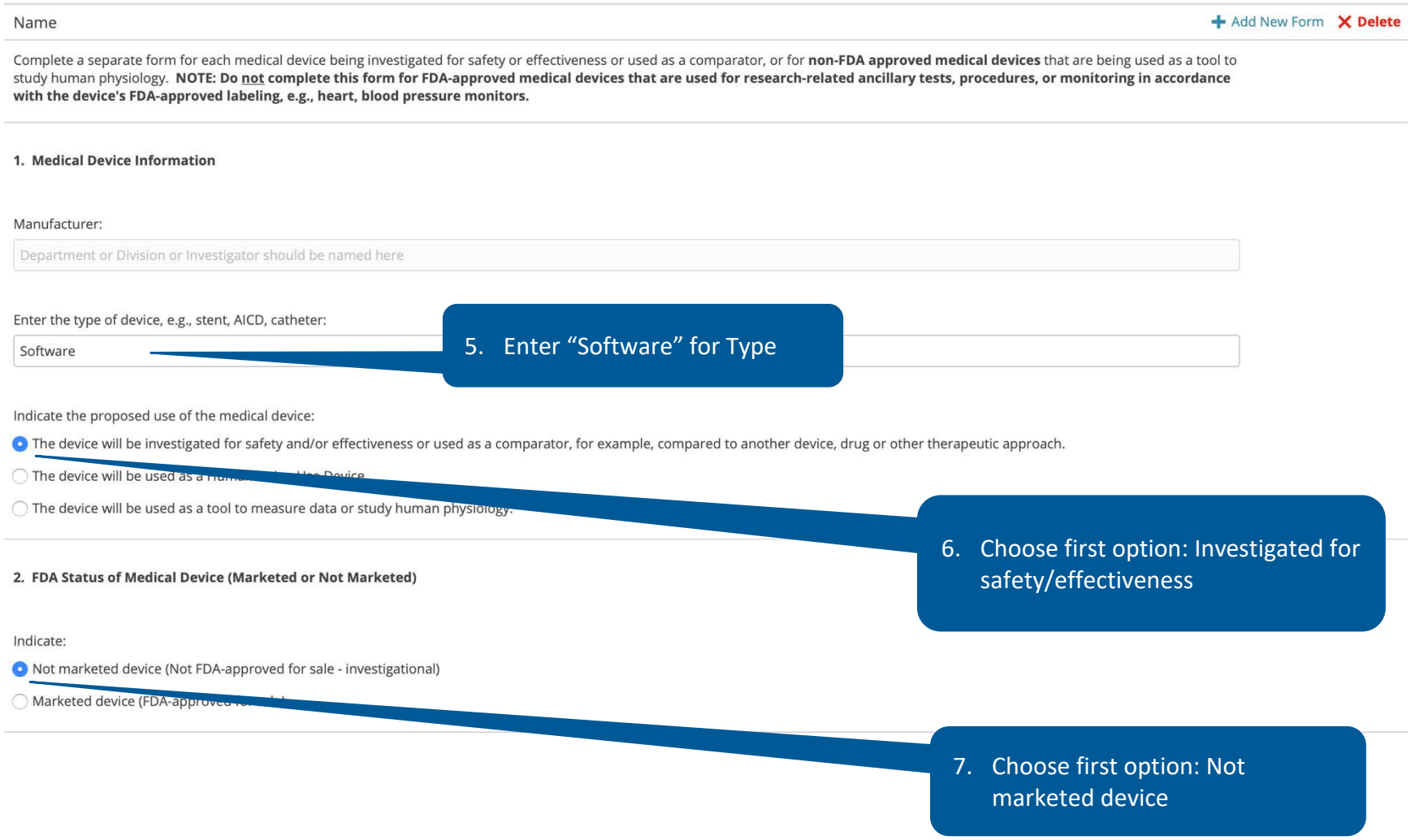
4. Navigate to or click on the “**Medical Devices**” form in your Insight application. Complete the name of the device, and any proprietary and/or common name for the device. In the “Manufacturer” field enter the Department, Division or Investigator name under which the software is being developed.



5. In the “Type” field – enter “Software”

6. For the “Proposed Use” choose the first answer “The device will be investigated for safety and/or effectiveness…”

7. For “FDA Status of Medical Device….” choose the first option “Not marketed device…”



Step 2: Choose the appropriate path based on the Guidance for Deploying Medical Image-based Software – including Algorithms – in the Clinical Setting document.

Path A: Your Study is EXEMPT from the IDE Requirement *(See Section C.1 of Guidance)*

Path B: Your study does NOT meet Exempt criteria, but may qualify as a "nonsignificant risk" device *(See Section C.2 of Guidance)*

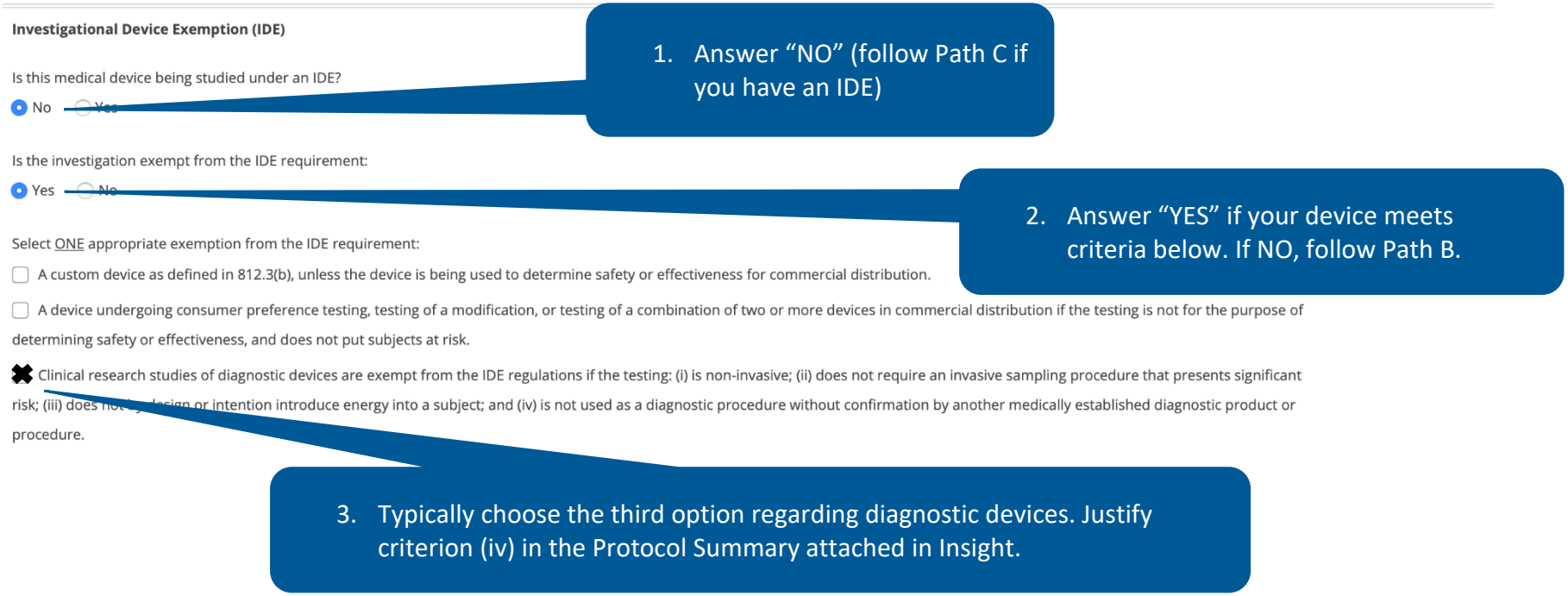
Path C: Your study already has an IDE assigned from the FDA

Path A: Your study meets the Exempt criteria

1. Under “Investigational Device Exemption (IDE)” answer “NO”

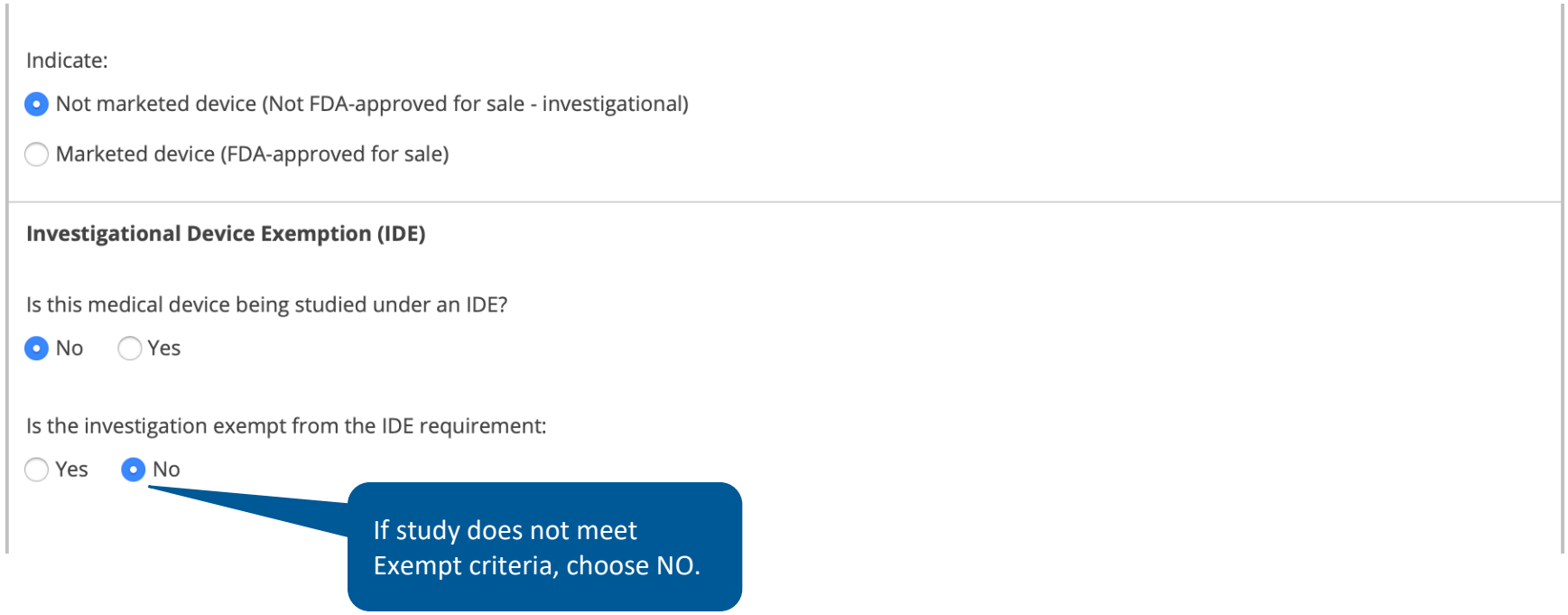
2. Under “is the investigation exempt from the IDE requirement?” answer “YES”

3. Under the “Select ONE appropriate exemption…” typically the third option applies. **IMPORTANT NOTE** A key criterion that must be met here is criterion (iv). *Be sure to describe in detail in the Protocol Summary the medically established diagnostic procedure that is being used to confirm the diagnosis provided by the software.*

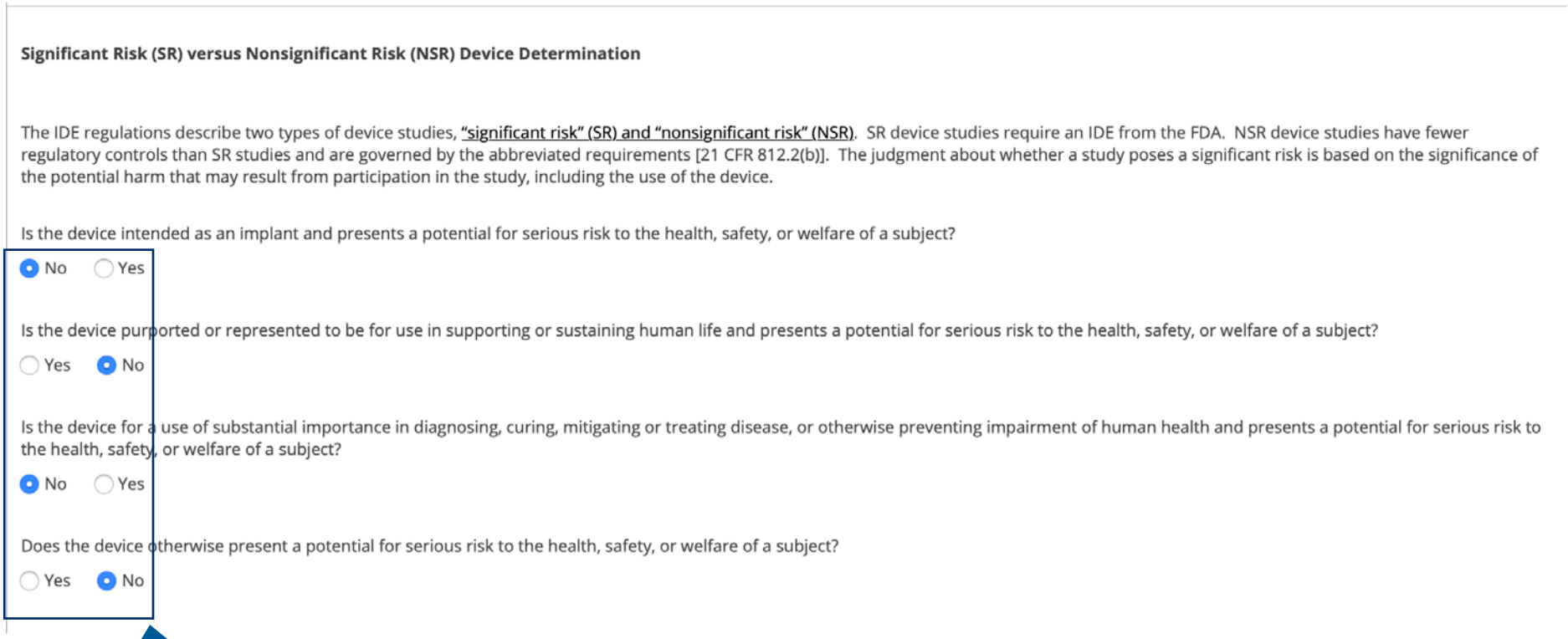


Path B: Your Study is NOT EXEMPT from the IDE Requirement and the IRB needs to make a Significant Risk/Nonsignificant Risk determination (*See Section C.2 of Guidance)*

1. If your study does not already have an IDE from the FDA *and* it does not meet the criteria in Step 2 for Exempt, choose "NO" to the question "Is the investigation exempt from the IDE requirement?" This means you are asking the IRB to consider whether this is a "nonsignificant risk device" for the way it will be used in this study and thus will NOT need an IDE.



2. Answer the questions as appropriate in the next section. You will need to provide specific justification in the Protocol Summary attached in the Insight application as to *why* the software as used in the study does NOT present a potential for serious risk to the health, safety, or welfare of a subject. Consider the risks if the software does not perform as expected (i.e. false positives/false negatives.)



Significant Risk (SR) versus Nonsignificant Risk (NSR) Device Determination

The IDE regulations describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). SR device studies require an IDE from the FDA. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The judgment about whether a study poses a significant risk is based on the significance of the potential harm that may result from participation in the study, including the use of the device.

Is the device intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject?

(•) No ( ) Yes

Is the device purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject?

( ) Yes (•) No

Is the device 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?

(•) No ( ) Yes

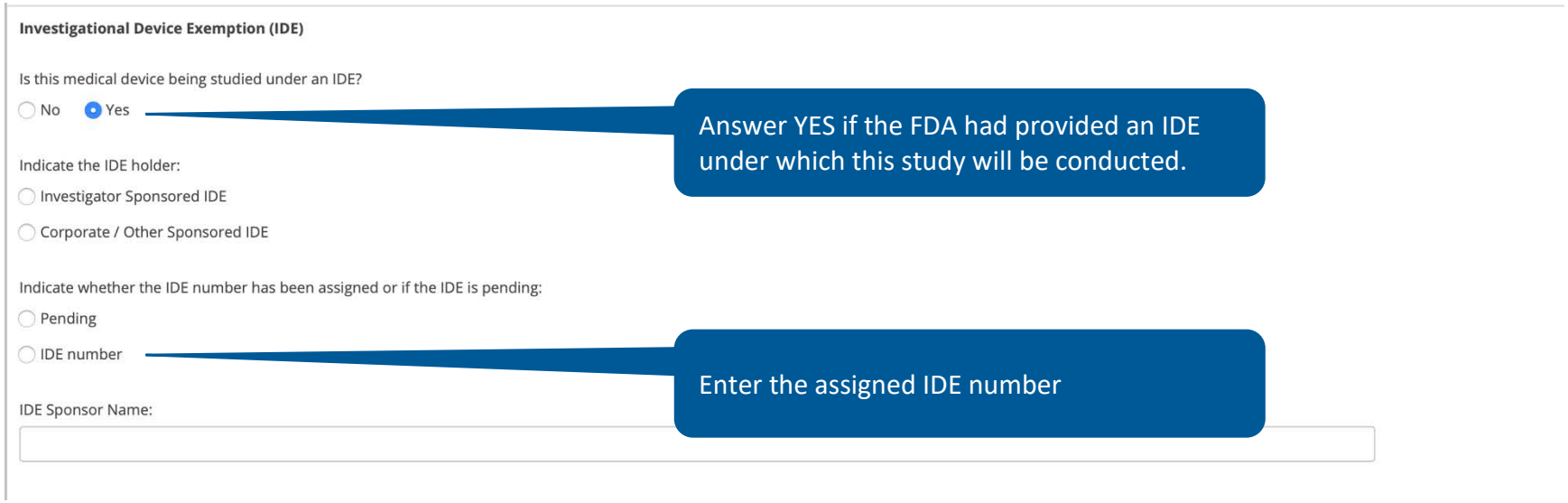
Does the device otherwise present a potential for serious risk to the health, safety, or welfare of a subject?

( ) Yes (•) No

This is how you would typically answer the questions, however, the PI should carefully assess each of these in the context of the use of the software in the study and provide specific justification regarding risk.

Path C: Your study already has an IDE assigned from the FDA

If you do have an IDE for the software, answer YES to “Is this medical device being studied under an IDE?” then answer the additional questions as appropriate.



Step 3: Complete the device tracking section: All AI Software Applications

The questions in this section are more applicable to individual investigational devices.
For AI software applications, put the following phrase in each box:
"Not applicable – device is an AI software application used via an internal system – it is not distributed to individual participants."

To whom are the devices shipped, and where are they stored?

What procedures are in place for ensuring that the investigational devices are only used by the investigators participating in this research for this investigation?

What is the plan for disposition of unused investigational devices at the conclusion of the study?

Who is responsible for completing the device accountability log and for disposition of unused devices at the conclusion of the study?