

**Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT)  
Under 42 CFR 11.22(b) for Clinical Trials Initiated on or After January 18, 2017<sup>1</sup>  
(NOT FOR SUBMISSION<sup>2</sup>)**

Instructions: Answer the following questions to evaluate whether the study is an applicable clinical trial (ACT). Use the accompanying "Elaboration" for additional information to help answer the questions.

Question	Yes	No
<b>1. Is the study interventional (a clinical trial)?</b> <i>Study Type</i> data element is "Interventional"	<input type="checkbox"/>	<input type="checkbox"/>
<b>2. Do ANY of the following apply (is the answer "Yes" to <u>at least one</u> of the following sub-questions: 2a, 2b, OR 2c)?</b>	<input type="checkbox"/>	<input type="checkbox"/>
<b>a. Is at least one study facility located in the United States or a U.S. territory?</b> <i>Facility Location – Country</i> data element is "United States," "American Samoa," "Guam," "Northern Mariana Islands," "Puerto Rico," "U.S. Virgin Islands," or other U.S. territory.		
<b>b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)?</b> <i>U.S. Food and Drug Administration IND or IDE Number</i> data element is "Yes."		
<b>c. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?</b> <i>Product Manufactured in and Exported from the U.S.</i> data element is "Yes."		
<b>3. Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)?</b> <i>Studies a U.S. FDA-regulated Device Product</i> data element is "Yes" and/or <i>Studies a U.S. FDA-regulated Drug Product</i> data element is "Yes."	<input type="checkbox"/>	<input type="checkbox"/>
<b>4. Is the study <u>other than</u> a Phase 1 trial of a drug and/or biological product or is the study <u>other than</u> a device feasibility study?</b> For drug product trials, <i>Study Phase</i> data element is NOT "Phase 1" and for device product trials, <i>Primary Purpose</i> is NOT "Device Feasibility."	<input type="checkbox"/>	<input type="checkbox"/>

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT that is required to be registered under 42 CFR 11.22.

<sup>1</sup> All pediatric postmarket surveillance studies of a device product as required by U.S. FDA under section 522 of the FD&C Act and for which FDA approved the plan on or after January 18, 2017 meet the definition of an ACT in 42 CFR Part 11.22(b) and are subject to the final rule requirements.

<sup>2</sup> The outcome generated by the checklist tool will not be retained by the Agency and will not be binding on either the user or any Government agency in any future actions.

## Elaboration: Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) Under 42 CFR 11.22(b) for Clinical Trials Initiated on or After January 18, 2017

The final rule for [Clinical Trials Registration and Results Information Submission \(42 CFR Part 11\)](#) specifies requirements for submitting clinical trial information to ClinicalTrials.gov. The “Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT)” (or “ACT Checklist”) and this elaboration is intended to assist users in evaluating whether a clinical trial or study is considered to meet the definition of an ACT, as specified in 42 CFR 11.22(b), and is subject to “expanded” registration requirements under the final rule.

### General Considerations

- 1. Definition of ACT.** Under the Final Rule, which implements Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), two types of ACTs are defined:
  - *Applicable device clinical trial:* (1) a prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes); (2) a pediatric postmarket surveillance of a device product as required under section 522 of the FD&C Act (21 U.S.C. 3601); or (3) a clinical trial of a combination product with a device primary mode of action under 21 CFR Part 3, provided that it meets all other criteria of the definition under this part. [Source: 42 CFR 11.10(a); 81 FR 65139]
  - *Applicable drug clinical trial:* a controlled clinical investigation, other than a phase 1 clinical investigation, of a drug product subject to section 505 of the FD&C Act (21 U.S.C. 355) or a biological product subject to section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), where “clinical investigation” has the meaning given in 21 CFR 312.3 and “phase 1” has the meaning given in 21 CFR 312.21. A clinical trial of a combination product with a drug primary mode of action under 21 CFR Part 3 is also an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. [Source: 42 CFR 11.10(a); 81 FR 65139]
- 2. Determination of ACT.** 42 CFR 11.22(b) sets forth an approach for determining whether or not a clinical trial initiated on or after January 18, 2017, meets the regulatory definitions of an applicable device clinical trial and an applicable drug clinical trial by identifying a series of specific criteria and the corresponding ClinicalTrials.gov registration data elements. [Source: 81 FR 65029]

Please note the following caveats:

- **Pediatric Postmarket Surveillance Studies of a Device Product.** While the ACT Checklist is intended to be used to evaluate clinical trials only, all pediatric postmarket surveillance studies involving a device product as required by U.S. FDA under section 522 of the FD&C Act and initiated on or after January 18, 2017, meet the definition of an ACT in 42 CFR Part 11.22(b) and are subject to “expanded” registration requirements under the final rule. *Pediatric postmarket surveillance of a device product* means the active, systematic, scientifically valid collection, analysis, and interpretation of data or other information conducted under section 522 of the FD&C Act (21 U.S.C. 360l) about a marketed device product that is expected to have significant use in patients who are 21 years of age or younger at the time of diagnosis or treatment. A pediatric postmarket surveillance of a device product may be, but is not always, a clinical trial. [Source: 42 CFR 11.10(a); 81 FR 65140]
- **Study Start Date on or After January 18, 2017.** The ACT Checklist is intended to be used to evaluate clinical trials initiated on or after January 18, 2017. An ACT is considered to be initiated on the date on which the first human subject is enrolled according to 42 CFR 11.22(a)(3) and is based on the *Study Start Date* data element, defined in part at 42 CFR 11.10(b)(16) as the actual date on which the first human subject was enrolled. As specified in 42 CFR 11.10(a), *enroll or enrolled* means a human subject’s, or their legally authorized representative’s, agreement to participate in a clinical trial following completion of the informed consent process, as required in

21 CFR Part 50 and/or 45 CFR Part 46, as applicable. For the purposes of this regulation, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol. [Source: 81 FR 65140]

## Specific Considerations

### 1. Is the study interventional (a clinical trial)?

*Study Type* data element is “Interventional.” [Sources: 42 CFR 11.22(b)(1)(ii)(A) & (b)(2)(i)]

*Study Type* is defined in the final rule as the nature of the investigation or investigational use for which clinical trial information is being submitted, e.g., interventional, observational. [Source: 42 CFR 11.10(b)(7); 81 FR 65140-41]

*Interventional* is defined in the final rule to mean, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes. [Source: 42 CFR 11.10(a); 81 FR 65140-41]

*Clinical Trial* is defined in the final rule as a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes. [Source: 42 CFR 11.10(a); 81 FR 65139]

### 2. Do ANY of the following apply?

#### A. Is at least one study facility located in the United States or a U.S. territory?

*Facility Location – Country* data element is “United States,” “American Samoa,” “Guam,” “Northern Mariana Islands,” “Puerto Rico,” “U.S. Virgin Islands,” or other U.S. territory. [Sources: 42 CFR 11.22(b)(1)(ii)(D)(1) and (b)(2)(iv)(A)]

The *Facility Location* data element is required for each participating facility in a clinical trial and includes information about the country in which participating facilities are located. [Source: 42 CFR 11.10(b)(31)(ii)]

#### Points to Consider:

- If a clinical study of a device product includes sites both within the United States (including any U.S. territory) and outside of the United States, and if any of those sites is using (for the purposes of the clinical study) a device product that is subject to section 510(k), 515, or 520(m) of the FD&C Act, we would consider the entire clinical study to be an applicable device clinical trial, provided that it meets all of the other criteria of the definition under this regulation. [Source: 81 FR 65013]
- If a clinical investigation of a drug product (including a biological product) includes sites both within the United States (including any U.S. territory) and outside of the United States, and any of those sites is using (for the purposes of the clinical investigation) a drug product or biological product that is subject to section 505 of the FD&C Act or section 351 of the PHS Act, we would consider the entire clinical investigation to be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this regulation. [Source: 81 FR 65015]
- If a sponsor of a clinical trial in a foreign country that does not meet the definition of an applicable clinical trial, and has an initiation date after the effective date of the regulations in 42 CFR Part 11, decides to add a location in the U.S. (or its territories), and as a result the trial meets the definition of an applicable clinical trial, the sponsor becomes subject to section 402(j) of the Public Health Service Act and 42 CFR Part 11. The requirements set forth in the regulation would need to be met, beginning with registration of the applicable clinical trial not later than 21 days after the enrollment of the first participant at the U.S. site. A clinical trial or study that, at any point in time, meets the conditions listed in 42 CFR 11.22(b)(1) or 11.22(b)(2), one of

which would be satisfied if there is at least one site location in the United States or U.S. territory, will be considered to meet the definition of an applicable clinical trial (emphasis added). [Source: 42 CFR 11.22(b)] Therefore, a clinical trial in a foreign country that otherwise meets the criteria in 42 CFR 11.22(b)(1) or 11.22 (b)(2) would become an applicable clinical trial when it adds the U.S. site. Clinical trial registration information would have to include information applicable to the entire trial, as is the case with all multi-site trials with information in ClinicalTrials.gov, because the entire clinical investigation is considered to be the applicable device or drug clinical trial. [Source: 81 FR 65013, 81 FR 65015]

**B. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)?**

*U.S. Food and Drug Administration IND or IDE Number* data element is “Yes” [Sources: 42 CFR 11.22(b)(1)(ii)(D)(3) and (b)(2)(iv)(C)]

The *U.S. Food and Drug Administration IND or IDE Number* data element provides an indication of whether there is an IND or IDE for the clinical trial. [Source: 42 CFR 11.10(b)(34)]

**Points to Consider:**

- Device products that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of an IDE is required under section 520(g) of the FD&C Act or non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b). [Source: 81 FR 65012]
- Drug products (including biological products) that are being studied under an IND are considered “subject to section 505 of the FD&C Act” both because (in most situations) the drug product being studied would need an approved NDA or licensed BLA to be marketed legally, and because INDs are issued by FDA pursuant to the authority in section 505(i) of the FD&C Act. [Source: 81 FR 65014]
- Furthermore, if a sponsor chooses to obtain an IND (issued under section 505 of the FD&C Act) for a clinical investigation of a drug product (including a biological product) that is not otherwise subject to section 505 of the FD&C Act or section 351 of the PHS Act, the sponsor, in so doing, agrees to regulation under section 505 of the FD&C Act, and that clinical investigation thus will be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. [Source: 81 FR 65015]

**C. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?**

*Product Manufactured in and Exported from the U.S.* data element is “Yes” [Sources: 42 CFR 11.22(b)(1)(ii)(D)(2) and (b)(2)(iv)(B)]

*Product Manufactured in and Exported from the U.S.* element means that any drug product (including a biological product) or device product studied in the clinical trial is manufactured in the United States or one of its territories and exported for study in a clinical trial in another country. [Source: 42 CFR 11.10(b)(15)]

**Points to Consider:**

- If the device product is manufactured in the United States or any U.S. territory, and is exported for study in another country (whether it is exported under section 801(e) or section 802 of the FD&C Act), the device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. If the device product is manufactured outside of the United States or its territories, and the clinical study sites are all outside of the United States and/or its territories, the device product would not be considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. A device product that is packaged and/or labeled in the United

States would be considered “manufactured” in the United States subject to section 510(k), 515, or 520(m) of the FD&C Act. [Source: 81 FR 65013]

- If the drug product (including a biological product) is manufactured in the United States or any U.S. territory, and is exported for study in another country under an IND (whether pursuant to 21 CFR 312.110 or section 802 of the FD&C Act), the drug product or biological product is considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act (as applicable), and the clinical investigation may be an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part. A drug product that is packaged and/or labeled in the United States would be considered “manufactured” in the United States subject to section 505 of the FD&C Act or section 351 of the PHS Act. [Source: 81 FR 65015]
- The term "manufacture" is used as a short-hand for all device or drug activities within FDA's jurisdiction. [Source: 81 FR 65011, 81 FR 65014] Therefore, any step in the manufacturing of the device or drug product (including device components, drug active ingredients, and packaging/labeling) that occurs in the United States (or one of its territories) would be considered "manufactured" in the United States.
- One of the criteria that must be met for a study to be an applicable clinical trial would be satisfied where the drug, biological, or device product "under investigation is a Product Manufactured in and Exported from the U.S. or one of its territories for study in another country." [42 CFR 11.22(b)(1)(ii)(D)(2) and 42 CFR 11.22(b)(2)(iv)(B)] The drug, biological, or device product "under investigation" as described in 42 CFR 11.22(b)(1)(ii)(D)(2) and 42 CFR 11.22(b)(2)(iv)(B) includes products that are used in the clinical trial in conjunction with, or compared to, each other. If a drug, biological, or device product is tested in conjunction with, or compared to, one or more other drug, biological, or device products (including a placebo or sham), then the products would be considered "under investigation" for purposes of this ACT condition.

### 3. Does the study evaluate at least one U.S. FDA-regulated drug, biological, or device product?

*Studies a U.S. FDA-regulated Device Product* data element is “Yes” and/or *Studies a U.S. FDA-regulated Drug Product* data element is “Yes.” [Sources: 42 CFR 11.22(b)(1)(ii)(C) & (b)(2)(iii)]

These data elements are defined as follows:

*Studies a U.S. FDA-regulated Device Product* means that a clinical trial studies a device product subject to section 510(k), 515, or 520(m) of the FD&C Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)). [Source: 42 CFR 11.10(b)(38); 81 FR 65143]

A device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act if any of the following is required before it may be legally marketed in the United States: (1) a finding of substantial equivalence under section 510(k) of the FD&C Act, (2) an order under section 515 of the FD&C Act approving a premarket approval application (PMA) for the device product, or (3) an HDE under section 520(m) of the FD&C Act. Device products that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include significant risk devices for which approval of an IDE is required under section 520(g) of the FD&C Act, non-significant risk devices that are considered to have an approved IDE in accordance with 21 CFR 812.2(b), or device products that are exempt from the submission requirements of 21 CFR part 812. [Source: 81 FR 65012]

A clinical study of a device product that is being conducted entirely outside of the United States (i.e., does not have any sites in the United States or in any U.S. territory) and is not conducted under an IDE may not be a clinical study of a device product subject to section 510(k), 515, or 520(m) of the FD&C Act and, therefore, is not an applicable device clinical trial, depending on where the device product being used in the clinical study is manufactured. If the device product is manufactured outside of the United States or its territories, and the clinical study sites are all outside of the United States and/or its territories, the device product would not be considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act. [Source: 81 FR 65013]

Therefore, a study record that (1) does not list “United States” (or a U.S. territory) for the Facility Information/Country data element, (2) lists “No” for the U.S. Food and Drug Administration IND or IDE data

element, and (3) lists “No” for the Product Manufactured in and Exported from the U.S. data element, would indicate that a studied device product is not “subject to” section 510(k), 515, or 520(m) of the FD&C Act. For such a study, the responsible party would list “No” for the Studies a U.S. FDA-regulated Device Product data element and the study would not be considered an applicable device clinical trial. Note that even if the device product being studied had previously been approved or cleared by the U.S. FDA under section 510(k), 515, or 520(m) of the FD&C Act for marketing in the U.S., that responsible party would list “No” for the Studies a U.S. FDA-regulated Device Product data element because the particular device product used in that study is not subject to those sections of the FD&C Act.

Regarding combination products, FDA regulations in 21 CFR part 3 specify that the primary mode of action of a combination product is the single mode of action that provides the most important therapeutic action of the intended therapeutic effects of the combination product. A study of a combination product with a device primary mode of action under 21 CFR part 3 would be considered an applicable device clinical trial, provided that it meets all other criteria of the definition under 42 CFR 11.10(a). We note that for such trials, the responsible party must indicate that the trial Studies a U.S. FDA-regulated Device Product. [Source: 81 FR 65014 and 65040]

#### Points to Consider:

- Device products may be used in clinical trials even though they are not the intervention studied in the clinical trial or the experimental variable of interest in the study. For example, clinical trials of procedures involving surgical device products may not be designed to study the effect of those device products. Therefore, when considering whether a clinical trial Studies a U.S. FDA-regulated Device Product a responsible party should consider whether (a) the study is designed to examine the effect or performance of an FDA-regulated device product or differences in the intended use, for example, variations in frequency of use, method of administration, design specifications, and other characteristics (e.g., used in one or more, but not all, arms in a multi-arm study); and/or (b) at least one pre-specified primary or secondary outcome measure reflects a characteristic, effect, or performance of an FDA-regulated device product (e.g., need for replacement or maintenance of the device). [Source: 81 FR 65040]
- Many radiation-emitting device products are subject to section 510(k) of the FD&C Act and some are subject to section 515 of the FD&C Act. If the product 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, it may meet the requirements for a humanitarian use device, under section 520(m) of the FD&C Act. FDA’s regulation in 21 CFR Part 892 describes the legal status (i.e., “classification”) of specific radiology devices, including diagnostic and therapeutic devices. For example, magnetic resonance diagnostic devices and medical charged-particle radiation therapy systems are designated in 21 CFR 892.1000 and 21 CFR 892.5050, respectively, as Class II devices (as defined in 21 CFR 860.3(c)(2)) and are subject to section 510(k) of the FD&C Act. In addition, an individual radiology device that is a “high risk” device and has been found by FDA to be not substantially equivalent (NSE) to an existing Class I, II, or III device must generally be approved by FDA under section 515 of the FD&C Act before marketing.
- The determination of whether the study of a specific device product is an applicable device clinical trial does not depend on the product’s device classification in 21 CFR 860.3(c) (i.e., Class I, II, or III). The relevant question is whether the device product must receive a finding of substantial equivalence under section 510(k) of the FD&C Act, an order under section 515 of the FD&C Act approving a pre-market approval application for the device product, or an HDE under section 520(m) of the FD&C Act. Most Class I devices, but not all, are exempt from the requirements for a finding of substantial equivalence under section 510(k) of the FD&C Act and do not require a premarket approval order under section 515 of the FD&C Act. By contrast, most Class II and all Class III devices require either clearance under section 510(k) of the FD&C Act or premarket approval under section 515 of the FD&C Act.

*Studies a U.S. FDA-regulated Drug Product* means a clinical trial studies a drug product (including a biological product) subject to section 505 of the FD&C Act (21 U.S.C. 355) or section 351 of the PHS Act (42 U.S.C. 262). [Source: 42 CFR 11.10(b)(38); 81 FR 65143]

This definition is interpreted to mean that the clinical trial studies a drug that is the subject of an approved NDA [new drug application] or BLA [biologic license application] or that would require an approved NDA or BLA to be legally marketed in the United States. A non-prescription drug product that is or could be marketed under an existing over-the-counter drug monograph (see 21 CFR 330–358) is not considered “subject to section 505 of the [FD&C Act].” [Source: 81 FR 65041]

A clinical investigation of a drug product (including a biological product) that is being conducted entirely outside of the United States (i.e., does not have any sites in the United States or in any U.S. territory) may not be a clinical investigation of a drug product or biological product subject to section 505 of the FD&C Act or section 351 of the PHS Act, and therefore not an applicable drug clinical trial, depending on where the drug product (including biological product) being used in the clinical investigation is manufactured. If the drug product (including a biological product) is manufactured outside of the United States or its territories, the clinical investigation sites are all outside of the United States, and the clinical investigation is not being conducted under an IND, the drug product or biological product would not be considered to be subject to section 505 of the FD&C Act or section 351 of the PHS Act, and the clinical investigation would not be an applicable drug clinical trial. [Source: 81 FR 65015]

Therefore, a study record that (1) does not list “United States” (or a U.S. territory) for the Facility Information/Country data element, (2) lists “No” for the U.S. Food and Drug Administration IND or IDE data element, and (3) lists “No” for the Product Manufactured in and Exported from the U.S. data element, would indicate that a studied drug or biologic product is not “subject to” section 505 of the FD&C Act or section 351 of the PHS Act. For such a study, the responsible party would answer “No” to the Studies a U.S. FDA-regulated Drug Product data element and the study would not be considered an applicable drug clinical trial. Note that even if the drug or biologic product being studied had previously been approved by the U.S. FDA under section 505 of the FD&C Act or section 351 of the PHS Act for marketing in the U.S., that responsible party would list “No” for the Studies a U.S. FDA-regulated Drug Product data element because the particular drug or biological product used in that study is not subject to those sections of the FD&C Act or PHS Act.

Regarding combination products, FDA regulations in 21 CFR part 3 specify that the primary mode of action of a combination product is the single mode of action that provides the most important therapeutic action of the intended therapeutic effects of the combination product. A study of a combination product with a drug primary mode of action under 21 CFR part 3 would be considered an applicable drug clinical trial, provided that it meets all other criteria of the definition under 42 CFR 11.10(a). We note that for such trials, the responsible party must indicate that the trial Studies a U.S. FDA-regulated Drug Product. [Source: 81 FR 65014 and 65041]

#### Points to Consider:

- A clinical trial for which the responsible party indicates the Intervention Type to be “dietary supplement” or “genetic” or “procedure” could in fact be an applicable drug clinical trial studying a drug product subject to section 505 of the FD&C Act or a biological product subject to section 351 of the PHS Act. For example, a product otherwise marketed as a dietary supplement could be studied for the treatment of cancer, or a genetic trial could study a gene therapy. [Source: 81 FR 65041]
- A clinical trial may include an FDA-regulated drug product even though the drug product is not a variable of interest. For example, a clinical trial of a device product may involve the surgical insertion of the device product under anesthesia, but the anesthesia drug product is not studied in the clinical trial. In determining whether a clinical trial studies a U.S. FDA-regulated drug product, a responsible party should consider whether (a) the clinical trial is designed to examine the effect of the FDA-regulated drug product(s) or of differences in the intended use, including differences in dosing, frequency of use, or

route of administration; and/or (b) at least one of the pre-specified primary or secondary outcome measures reflects a characteristic or effect of the FDA-regulated drug product(s). [Source: 81 FR 65041]

#### 4. Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study?

For drug trials, *Study Phase* data element is NOT “Phase 1” and for device trials, *Primary Purpose* is NOT “Device Feasibility.” [Sources: 42 CFR 11.22(b)(1)(ii)(B) & (b)(2)(ii)]

These data elements are defined as follows:

*Study Phase* means, for a clinical trial of a drug product (including a biological product), the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, such as phase 2 or phase 3, and in 21 CFR 312.85 for phase 4 studies. [Source: 42 CFR 11.10(b)(6); 81 FR 65141]

Under 21 CFR 312.21(a)(1), a phase 1 study “includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During phase 1, sufficient information about the drug’s pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, phase 2 studies. The total number of subjects and patients included in phase 1 studies varies with the drug, but is generally in the range of 20 to 80.” Under 21 CFR 312.21(a)(2), “[p]hase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.” Clinical trials that are phase 1 studies under 21 CFR 312.21 are not applicable drug clinical trials. [Source: 81 FR 65015-16]

#### Points to Consider:

- Although we are aware that the term “phase 0” is used in practice (e.g., to refer to clinical trials that are exploratory in nature and are not designed to evaluate therapeutic or diagnostic intent), any trial that would be referred to as “phase 0” meets the definition of a phase 1 trial under FDA regulations (21 CFR 312.21). [Source: 81 FR 65036]
- Clinical trials that are identified as phase 1/phase 2 trials (i.e., trials with characteristics of both phase 1 and phase 2 studies) are not considered phase 1 studies and may be applicable drug clinical trials if they meet the other specified criteria. [Source: 81 FR 65016]
- A bioequivalence or comparative bioavailability study that falls within the scope of 21 CFR 320.24(b)(1), (2), or (3) shares many of the characteristics of a phase 1 study and is considered to be a phase 1 trial (and, therefore, not an applicable clinical trial) in this rule. [Source: 81 FR 65016]

*Primary Purpose* means the main objective of the intervention(s) being evaluated by the clinical trial. [Source: 42 CFR 11.10(b)(4); 81 FR 65141]

Regarding the options available under *Primary Purpose*, “device feasibility” should *only* be selected when a device product is being evaluated for the feasibility of the product or of a test prototype device and not health outcomes. Other options include “treatment,” “prevention,” “diagnostic,” and “screening.” [Source: 81 FR 65035]

Small clinical trials to determine the feasibility of a device product, or clinical trials to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes, are excluded from the definition of an applicable clinical trial. [Source: 42 CFR 11.10(a)] Our explanation of this exemption [for “device feasibility” from the definition of applicable device clinical trial] is consistent with FDA’s regulation



of devices. FDA published the guidance [Investigational Device Exemptions \(IDEs\) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human \(FIH\) Studies](#) (October 2013) to address the development and review of IDE applications for early feasibility studies of significant risk devices. For the purposes of the guidance, the guidance defines an “early feasibility study” as a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication. The guidance further defines a “traditional feasibility study” as a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. Section 402(j)(1)(A)(ii)(I) of the PHS Act excludes “small clinical trial[s] to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes” from the definition of “applicable device clinical trial.” The excluded clinical trials described in this statutory definition appear to be consistent with the early feasibility study definition in the guidance, but not with that of the traditional feasibility study, which evaluates preliminary safety and effectiveness information (i.e., for “health outcomes”). Therefore, it is likely that only early feasibility studies would fall within this exclusion under the § 11.10 definition of an “applicable device clinical trial.” [Source: 81 FR 65011] In addition, although the regulation does not specify a threshold number, a trial with at least 10 subjects would generally not be considered “small” for purposes of the exclusion. [Source: 81 FR 65011]

## History of Changes

2016-12-14: Original version

2017-06-14: Elaboration re-ordered and expanded to integrate information made available on the ClinicalTrials.gov Frequently Asked Questions Web page (accessible from: <https://prsinfo.clinicaltrials.gov>). Checklist re-ordered.

2017-10-19: Elaboration expanded to integrate information about radiation-emitting device products and device product classes made available on the ClinicalTrials.gov Frequently Asked Questions Web page (accessible from: <https://prsinfo.clinicaltrials.gov>).

2017-10-20: Corrected document to add text from 2017-06-14 version that was inadvertently removed with the 2017-10-19 update.