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 (NOT FOR SUBMISSION)

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
1. Is the study interventional (a clinical trial)? Study Type š o u v š] • ^ / v š Œ À v š] } v o _		
2. } E z } (š Z (} o o } Á] v P ‰ ‰ o Ç ~] • š Z v • Á Œ ^ z • _ š		

Elaboration

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 š o u v 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(f); 81 FR 65140]

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]

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 š o u v š] • ^ h v] š ^ š š • U _ ^ u Œ] v ^ u } U _ ^ ' µ u U _ / • o v • U _ ^ W µ Œ š } Z] } U , or other U.S. jurisdiction. [Source: v •

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 š o u v š] [Source: 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)(3)(4)]

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 mdaa0-6(((()-3(1)7(1)77

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^š š • Á}µo }v•] Œ ZZu vµ(šµŒ [[ ]v šZ hv]š ^š š • •µ i 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 other criteria of the definition under this part. A drug ‰Œ} µ š šZ š]• ‰ l P v l}Œ o o]v šZ hv]š ^š š • Á}µo 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 shorthand 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, biologic or device (as defined in 42 CFR

2 CFR 11.22BT /(u)-3(d) in 42 CFR

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 not select Yes for the 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). 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. [• Œ P µ o š] } v] v î í & Z W Œ š ô õ î • Œ] ~] X X U ^ o • •] ( ] š] } v _ • } (• ‰] ( ] Œ] } o } P Ç À] • U] v o µ] v P] 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 ment

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 ô •] • v } š } v •] Œ ^ • µ i š š } • € & ˜ [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]

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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 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(b). 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

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- ¶ A clinical trial may include an FDA-regulated drug product even though the drug product i 612 792 re 2 nouc

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?

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 ‰ µ Œ ‰ } • • } (š Z P µ] v U š Z P µ] v ( ] v • v ^ Œ o Ç (•]] o] š Ç • š device early in development, typically before the device design has been finalized, for a specific indication. The P µ] v (µ Œ š Z Œ ( ] v • ^ š Œ] š] } v o (•]] o] š Ç • š µ Ç _ • o] v] o capture preliminary safety and effectiveness information on a near-final or final device design to adequately ‰ o v v ‰ ‰ Œ } ‰ Œ] š ‰] À } š o • š µ Ç X ^ š] } v ð ì î ~ i • ~ í • ~ • ~]] • ~ / • } (š determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome u • µ Œ Œ o š • š } (•]] o] š Ç v v } š š } Z o š Z } µ š } u • _ (Œ } u š Z ( ] š Œ] o X _ d Z Æ o µ o] v] o š Œ] o • • Œ]] v š Z] • 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., (} Œ ^ Z o š Z } µ š } u • _ • X d Z Œ (} Œ U] š early feasibility studies would fall within this exclusion under the 21 CFR 812.3(o) definition of an applicable device o] v] o [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 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 reordered.

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 2016-12-14 version that was inadvertently removed with the 2017-10-19 update.