THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

ClinicalTrials.gov Frequently-asked Questions (FAQ)

What is ClinicalTrials.gov?
A web-based resource for patients, their families, health care professionals, researchers and the public with access to information on publicly and privately funded clinical studies. Clinicaltrials.gov is the largest registry in the world.

Which trials must be registered on ClinicalTrials.gov?
Registration is required for studies that meet the definition of an "applicable clinical trial" (ACT) and either were initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007. Please see Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) ("ACT Checklist"), which follow the criteria specified in 42 CFR 11.22(b), to determine whether a study initiated on or after January 18, 2017, is an ACT subject to the expanded registration requirements under the Final Rule.

Why is it important to register and report results on ClinicalTrials.gov?
Clinical trials are not abstract research projects; they are large, expensive, practical evaluations that aim to directly inform clinical practice. Efforts to synthesize evidence into systematic reviews or inform guidelines are compromised by missing trial data. Patients and clinicians cannot make informed choices when the results of clinical trials are routinely withheld. Liberati A. An unfinished trip through uncertainties. BMJ 2004; 328: 531

Failure to report the results of a clinical trial can distort the evidence base for clinical practice, breaches researchers' ethical obligations to participants, and represents an important source of research waste. Moher D, Glasziou P, Chalmers I, et al. Increasing value and reducing waste in biomedical research: who's listening? Lancet 2016; 387: 1573–86.

Why must studies be registered on ClinicalTrials.gov?
It is required by law: The Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) defines the regulatory requirements and procedures for submitting registration and results information for certain clinical trials to ClinicalTrials.gov, in accordance with Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801). The Final Rule has been in effect since January 18, 2017.

It is required for certain journals: The International Committee of Medical Journal Editors (ICMJE) requires trial registration as a condition of the publication of research results generated by a clinical trial. To fulfill this obligation organizations and individuals can provide the World Health Organization (WHO) Trial Registration Data Set required by ICMJE to ClinicalTrials.gov or a WHO primary registry. The ICMJE expects authors to meet all results reporting requirements of their funding and regulatory agencies. If there

are no such reporting requirements, the ICMJE encourages authors to submit results information to the same database on which their trials are registered.

What is the responsibility of the Institutional Protocol Registration System Administrator (IPRSA)?

- Release study records as needed
- Review records for compliance (i.e. updated within one year, results submitted on time, queries addressed and answered by responsible party)
- Notify responsible party of noncompliance and help reduce noncompliant problem records
- Create/disable user accounts, reset passwords
- Transfer records as needed

Who is the Responsible Party (RP)?

If a study was initiated and written by an investigator at Ohio State, the Principal Investigator (PI) of the study should be listed as the Responsible Party, whether listed as “Principal Investigator” or “Sponsor-Investigator.”

What are the responsibilities of the RP?

- Register the trial on ClinicalTrials.gov and submit results
- Update the record, minimally, on an annual basis

How often should records be updated?

The study record needs to be updated at least once a year, with some data elements requiring more rapid updates, until the study is completed and/or the PRS Review process has ended for submitted results information.

What is a problem record?

Records may have issues with data entry errors or FDAAA 801. Records may have not been updated recently or have missing information. FDAAA results may be late, incomplete, or missing information. A user can view the problems associated with a record in the Problems column within a ClinicalTrials.gov record.

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Which Ohio State internal department provides ClinicalTrials.gov administrator contact information?

The Center for Clinical and Translational Science (CCTS) maintains several documents regarding ClinicalTrials.gov registration and contact information ClinicalTrials.gov administrators. The Office of Responsible Research Practices (ORRP) also maintains contact information for Ohio State administrators.

How often does the ClinicalTrials.gov PRS send emails regarding problem records?
Problems notifications are sent twice yearly (approximately every six months) to each organization. These notifications are sent to Record Owners, Responsible Parties, and the organization's Administrator(s), alerting them to their records that list any type of record problem.

A PI departed/joined Ohio State. How do I transfer a record to/from a different institution?
Email the ClinicalTrials.gov PRS at register@clinicaltrials.gov and they can provide the contact information for the administrators at the other institution. The other institution must agree to the transfer. To coordinate a transfer, you must include the following information: Study title, NCT #, organization, and new record owner. After obtaining this information, email the ClinicalTrials.gov PRS and they can complete the transfer.

Where can I find ClinicalTrials.gov training?
The Collaborative Institutional Training Initiative (CITI) offers, *ClinicalTrials.gov Registration and Results Summary Disclosure in ClinicalTrials.gov.* This course provides a video-enhanced guide to compliance with the FDAAA Final Rule and NIH Policy on clinical trial disclosure in ClinicalTrials.gov. The course guides learners through critical parts of the regulations and provides a step-by-step guide to data entry, thus helping organizations avoid the risk of significant civil monetary penalties or loss of NIH grant funding. Ohio State does not subscribe to this course, and as such, there is an independent learner fee associated. https://www.citiprogram.org/.

The ClinicalTrials.gov Protocol Registration and Results System (PRS) has PRS Guided Tutorials to provide step-by-step instructions for entering registration and results information. https://prsinfo.clinicaltrials.gov/tutorial/content/index.html#/

What is the ClinicalTrials.gov Taskforce?
The Clinical Trials Registration and Results Reporting Taskforce is a national consortium of members of academic medical centers, universities, hospitals, and non-profit organizations focused on the implementation of domestic clinical trials registration and results reporting requirements in the ClinicalTrials.gov public repository. The objectives of the group are to identify best practices, develop solutions and tools for regulatory support and investigators, and serve as a communication forum. To join, complete a membership form on their website. https://ctrrtaskforce.org/

Who is subject to fines for noncompliance with ClinicalTrials.gov?
Responsible Parties who violate regulations and fail to submit clinical trial registration and/or results are subject to financial penalties. Violations not corrected within 30 days following notification may be fined up to $12,103 (adjusted in 2019 for inflation) each day until the violation is corrected.

Who may I contact with questions regarding ClinicalTrials.gov?
The ClinicalTrials.gov staff quickly responds to emails at register@clinicaltrials.gov.

Frequently Asked Questions from ClinicalTrials.gov
https://clinicaltrials.gov/ct2/manage-recs/faq

General

Is there a charge for listing studies on ClinicalTrials.gov?
No, there is no charge for listing studies on ClinicalTrials.gov. ClinicalTrials.gov is a free service of the National Institutes of Health, provided through the National Library of Medicine.

My study is not yet approved by a human subjects review board (ethics review committee, institutional review board). Can I enter it on ClinicalTrials.gov?
Most studies require approval from a human subjects review board. If your study requires approval, you may register your study on ClinicalTrials.gov prior to getting approval if the overall recruitment status of the study is not yet recruiting (see Overall Recruitment Status data element on ClinicalTrials.gov)

If a study requires human subjects review board approval, approval must be obtained before the study's overall recruitment status is changed to Recruiting. When board approval is obtained, please update the Protocol Section of the study record in the Protocol Registration and Results System (PRS) and Release (submit) the study for processing.

See How to Register Your Study and How to Edit Your Study Record for more information.

My clinical trial evaluating a benign behavioral intervention is exempt human subjects research (HSR) per Exemption 3 outlined in 45 CFR 46. How do I indicate this exemption when registering the clinical trial at ClinicalTrials.gov?
Set the Human Subjects Protection Review Board Status data element to "Exempt". When you release your record, please also contact the ClinicalTrials.gov customer service team at register@clinicaltrials.gov to explain why you have selected exempt in the Human Subjects Protection Review Board Status field.

Why can't I find my study on ClinicalTrials.gov?
It might not have been released (submitted) to ClinicalTrials.gov for processing. After a record has been entered into PRS (or modified) and marked as Complete, it must be Approved and Released by the Responsible Party (see Responsible Party data element on ClinicalTrials.gov).

The study might also be undergoing review. After the Responsible Party Releases (submits) information to ClinicalTrials.gov, that information undergoes a manual review to identify possible errors, deficiencies, or inconsistencies that are not detected automatically during data entry. The Responsible Party will be notified of any issues that need correction, usually within a few days after release of the protocol information. The review of results information may take longer (up to 30 days).

See How to Register Your Study and How to Submit Your Results for more information.

When will the NCT Number for my study be assigned?
The NCT Number, also called the ClinicalTrials.gov Identifier, is assigned after the protocol information has been Released (submitted) by the Responsible Party and passed review by ClinicalTrials.gov staff. At that time an e-mail notification containing the NCT Number is sent. The record, including its NCT Number, will typically be available on ClinicalTrials.gov within 2–5 business days after it is released.

See How to Register Your Study for more information.

Can I register a study after it has started, has closed to recruitment, or has been completed?
Yes, you can register a study on ClinicalTrials.gov at any time. Please note that, in general, Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) requires Applicable Clinical Trials to be registered within 21 days of enrollment of the first participant. In addition, the International Committee of Medical Journal Editors and other journals require registration of clinical trials prior to enrollment of the first participant.

See FDAAA 801 and the Final Rule for more information.

Must clinical studies with no external sources of funding ("unfunded" studies) be registered on ClinicalTrials.gov?
The registration requirements of Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (PDF) and the International Committee of Medical Journal Editors (ICMJE) policy on Clinical Trial Registration under the ICMJE Recommendations do not exclude clinical studies with no external sources of funding ("unfunded" studies). See FDAAA 801 and the Final Rule for more information on which trials must be registered under FDAAA 801.

In general, an unfunded study should be registered via the PRS account of the Sponsor. When an investigator is considered the Sponsor (a Sponsor-Investigator), the study should be registered using the PRS account of the investigator's affiliated institution with the Responsible Party indicated as Sponsor-Investigator. ClinicalTrials.gov will then display the investigator as the Sponsor instead of the investigator's institution.

The Protocol Registration Data Element Definitions page on ClinicalTrials.gov describes the related data elements for Responsible Party.

How do I contact ClinicalTrials.gov if I have a question about my study record?
If you have questions or need help updating your record, e-mail register@clinicaltrials.gov. If the question is about a specific study record, please provide the NCT Number or the Unique Protocol ID (if an NCT Number has not yet been assigned). Please include enough information about the issue so that we may better assist you. We generally respond to all e-mails within 1 business day.

Do I need to register each single-patient investigational new drug application (IND) or protocol exception (including for emergency use) separately?
No, manufacturers or Sponsors accepting requests for single-patient investigational new drug applications (INDs) or protocol exceptions (including for emergency use) should provide only one expanded access record.

See the Registering Expanded Access Records section of the How to Register Your Study for more information.

Protocol Registration and Results System (PRS)

Can an organization have multiple users for a single account?
Yes. When sponsors or their representatives register to become PRS data providers, they will be given information on using PRS, including instructions for creating additional user accounts.

See How to apply for a PRS Account for more information.

Can registration and results information be uploaded electronically to ClinicalTrials.gov?
Yes. This option is available in PRS as an HTTP upload of an Extensible Markup Language (XML) file. After obtaining a PRS account, login to PRS and review the User's Guide for information on XML upload.

See How to apply for a PRS Account for help with obtaining a PRS account.

Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801)

To comply with FDAAA 801, must I submit information to ClinicalTrials.gov, or can I use another registry or results database?
You must use ClinicalTrials.gov to fulfill the requirements of FDAAA 801 (PDF). FDAAA 801 requires Responsible Parties to submit clinical trial information to the Director of the National Institutes of Health (NIH) for inclusion in the registry and results database established via ClinicalTrials.gov.

Does FDAAA 801 only apply to industry-sponsored studies?
No. FDAAA 801 applies to any clinical study that meets the definition of an Applicable Clinical Trial and that was initiated after September 27, 2007, or that was initiated on or before that date and was still ongoing as of December 26, 2007. FDAAA 801 does not distinguish between types of sponsors or funding sources in establishing requirements for registration and results submission.

For complete statutory definitions and more information on the meaning of Applicable Clinical Trial, see Elaboration of Definitions of Responsible Party and Applicable Clinical Trial (PDF).

Does the definition of applicable clinical trial under FDAAA 801 only include studies conducted under an FDA Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)?
No. A clinical investigation of a drug can be an Applicable Drug Clinical Trial under FDAAA 801 even if it does not require an IND, and a clinical investigation of a device can be an Applicable Device Clinical Trial whether or not an IDE is required.
See Elaboration of Definitions of Responsible Party and Applicable Clinical Trial (PDF) for more information.

Am I required to submit to ClinicalTrials.gov the results of a clinical trial that is not an applicable clinical trial?
Results submission is not required under FDAAA 801 for a clinical trial that is not an Applicable Clinical Trial (for example, a phase 1 trial studying an FDA-regulated investigational new drug). If a Responsible Party chooses to voluntarily submit results for such a trial, however, the Voluntary Submissions (PDF) provision of FDAAA 801 may apply.

Under the Voluntary Submissions (PDF) provision, a Responsible Party who submits results for such a clinical trial must submit complete clinical trial results information and must also submit results for each Applicable Clinical Trial that is required to be submitted to FDA under Sections 505, 510(k), 515, and 520(m) of the Federal Food, Drug, and Cosmetic Act or Section 351 of the Public Health Service Act for the same use studied.

How do I submit results information if the trial is terminated (that is, stopped prematurely) and no data were collected for one or more Outcome Measures?
If no participants were ever enrolled in the trial, set the Overall Recruitment Status to Withdrawn, and no further results information will need to be submitted.
For a trial that was terminated after participants were enrolled, provide any available data. If no data are available for any of the Outcome Measures, specify zero ("0") for the Number of Participants Analyzed in each Arm/Group, and leave the data fields blank. In this case, provide an explanation in the Analysis Population Description for why zero

participants were analyzed and, if appropriate, provide information in the Limitations and Caveats module. Even if data are not entered for Outcome Measures, submit the available data for the enrolled participants in the Participant Flow, Baseline Characteristics, and Adverse Events modules.

I completed a clinical trial that studied an investigational product (drug, biological product, or device that is not initially approved, licensed, or cleared by the FDA). There is no intent to seek approval, clearance, or licensure of the product by the FDA (for example, development of the investigational product has been terminated). How do I indicate that results need not be submitted for this trial?

The Responsible Party may Certify Initial Approval in the PRS. This indicates that the clinical trial was completed before a drug, biological product, or device studied in the trial was initially approved, licensed, or cleared by the FDA for any use.

Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11)

Applicable Clinical Trial

How do I determine if my study is an applicable clinical trial?
The Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) stated that a checklist-based tool would be available to assist Responsible Parties in evaluating whether their clinical trial or study is an applicable clinical trial (ACT) as defined in in 42 CFR 11.10(a) based on the conditions outlined in 42 CFR 11.22(b) (Determination of applicable clinical trial for a clinical trial or study initiated on or after January 18, 2017).

The Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (PDF) (June 2018) document follows the criteria specified in 42 CFR 11.22(b), as explained further in the preamble, to determine whether a study initiated ***on or after*** January 18, 2017, is an ACT subject to "expanded" registration requirements under the final rule.

Beyond their primary purpose, the ACT Checklist and Elaboration may also be useful to assist in evaluating whether a clinical trial or study that was initiated ***before*** January 18, 2017, and which is not subject to the final rule requirements, is an ACT under section 402(j) of the Public Health Service Act.

We note that Responsible Parties or other users of the ACT Checklist and Elaboration are responsible for using accurate data about a clinical trial or study and for properly evaluating whether the trial or study must be registered and, if so, which results must be submitted. The outcome generated from the ACT Checklist will not be retained by the

National Institutes of Health (NIH) and will not be binding on either the user or any government agency in any future action(s).

If a clinical trial is not an applicable clinical trial (ACT) at study initiation because it is conducted entirely outside the United States, but the trial subsequently opens a U.S. site, am I required to register the trial?

If a sponsor of a clinical trial in a foreign country that does not meet the definition of an ACT, 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 ACT, 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 ACT not later than 21 days after the enrollment of the first participant at the U.S. site. Per 42 CFR 11.22(b), "[a] clinical trial or study that, at any point in time, meets the conditions listed in paragraph (b)(1) or (2) of this section will be considered to meet the definition of an applicable clinical trial." Therefore, this trial would become an ACT when it adds the U.S. site. Clinical trial registration information must 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 (see 81 FR 65013, 81 FR 65015).

What is the definition of a drug, biological, or device product under investigation being "manufactured" in the United States?

The regulations define "applicable clinical trial" (ACT) in 42 CFR 11.10(a) and in 42 CFR 11.22 describe which ACTs are subject to the registration requirements. A clinical trial or study initiated on or after January 18, 2017, that meets certain conditions in 42 CFR 11.22(b)(1) or (2) will be considered to meet the definition of an applicable clinical trial. One of these conditions is whether 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 regulations also define the "Product Manufactured in and Exported from the U.S." in 42 CFR 11.10(b)(15) as meaning "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."

The agency explained that the term "manufacture" is used as a "short-hand for all device [or drug] activities within FDA's jurisdiction." (81 FR 65011 (device), 81 FR 65014 (drug)) 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.

In addition, 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.

How do I know if my clinical trial "Studies a U.S. FDA-regulated Drug Product" or "Studies a U.S. FDA-regulated Device Product" when evaluating whether it is an applicable clinical trial (ACT) subject to the regulation under the conditions specified in 42 CFR 11.22(b)? Specifically, for a trial conducted entirely outside the U.S.?

The regulation defines both "U.S. FDA-regulated device product" and "U.S. FDA-regulated drug product" in 42 CFR 11.10(a). This "FDA-regulated" concept is also part of the ACT definition under 42 CFR 11.10(a) and described in 42 CFR 11.22(b)(1)(ii)(C) and 42 CFR 11.22(b)(2)(iii) for an applicable device clinical trial and an applicable drug clinical trial initiated on or after January 18, 2017, respectively. The regulation further defines these specific concepts as data elements in 42 CFR 11.10(b)(38) ("Studies a U.S. FDA-regulated Device Product") and 11.10(b)(39) ("Studies a U.S. FDA-regulated Drug Product") and explains them as a device product "subject to" section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic (FD&C) Act and a drug product "subject to" section 505 of the FD&C Act or section 351 of the Public Health Service (PHS) Act, respectively. The Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (PDF) (June 2018) provides additional information about these definitions.

The Final Rule preamble addresses whether a studied product meeting the device definition is "subject to" section 510(k), 515, or 520(m) of the FD&C Act. The Final Rule preamble states: "[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." (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.

The Final Rule preamble also addresses whether a studied product meeting the drug definition is "subject to" section 505 of the FD&C Act or section 351 of the PHS Act. The Final Rule preamble states: "[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." (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.
Example: For a clinical study conducted entirely outside of the United States or its territories, in which the drug, biological, or device product is not studied under an IND or IDE, and the studied drug, biological, or device product is manufactured outside of the United States or its territories, then the studied product would not be considered "FDA-regulated" under the relevant condition in 42 CFR 11.22(b)(1)(ii)(C) and 11.22(b)(2)(iii). The responsible party of such a study would select "No" for the data elements of

Studies a U.S. FDA-regulated Drug Product and/or Studies a U.S. FDA-regulated Device Product (42 CFR 11.28(a)(2)(i)(N) and (O)).

For additional information, see also:

- National Institutes of Health (NIH): Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (PDF) (June 2018)

- FAQ: What is the definition of a drug, device, or biological product under investigation being "manufactured" in the United States?

Is a clinical trial that uses a radiation-emitting product considered to be a trial that "Studies a U.S. FDA-regulated Device Product" under 42 CFR Part 11?
To assess whether a clinical trial using a radiation-emitting product "Studies a U.S. FDA-regulated Device Product" for purposes of the applicable device clinical trial definition in 42 CFR 11.10(a), 42 CFR 11.10(b)(38), and 42 CFR 11.22(b)(ii)(C), consider whether the following conditions apply:

(1) the product meets the definition of a device under section 201(h) of the Federal Food, Drug, and Cosmetic Act (FDA&C Act); and
(2) the clinical trial "studies" a device product subject to section 510(k), 515, or 520(m) of the FD&C Act.

For this assessment, the first question is whether the product meets the "device" definition at section 201(h) of the FD&C Act, which is how the regulation at 42 CFR 11.10(a) defines "device." FDA has additional authority over radiation-emitting products under sections 531 - 542 of the FD&C Act; some are also devices, some are not. The assessment of whether a radiation-emitting product is a "device" under section 201(h) of the FD&C Act is largely dependent on its intended use. A radiation-emitting product such as external beam radiation used in a clinical trial would very likely be a "device" under 201(h) of the FD&C Act since it would likely be intended for use in the treatment, diagnosis, cure, prevention, or mitigation of disease or other conditions, and/or intended to affect the structure or function of the body.

If the product is a device under section 201(h) of the FD&C Act, then the second question is whether the clinical trial studies a device product subject to section 510(k), 515, or 520(m) of the FD&C Act. In explaining the "applicable device clinical trial" definition in 42 CFR 11.10(a), the Final Rule preamble clarifies that 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) permitting the device product to be marketed, (2) an order under section 515 of the FD[&]C Act approving a pre-market approval application for the device product, or (3) an HDE [or Humanitarian Device

Exemption] under section 520(m) of the FD[&]C Act." (81 FR 65012). In addition, for the clinical trial to be an "applicable device clinical trial," the trial must meet the definition at 42 CFR 11.10(a), its primary purpose must be other than a feasibility study, and it must meet one of the following conditions: (1) at least one study facility is located in the U.S. (or a U.S. territory); (2) the study is conducted under a U.S. Investigational Device Exemption (IDE); or (3) the device product is manufactured in and exported from the U.S. (or a U.S. territory). (42 CFR 11.22(b)(1)(ii)).

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 classified as a "high risk" class III device or 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 Final Rule preamble also explains that radiation-emitting products can be subject to the requirements in 42 CFR Part 11: "For example, a clinical trial for which a responsible party indicates the Intervention Type is 'radiation,' 'genetic,' or 'procedure' could in fact be an applicable device clinical trial studying a device product subject to section 510(k), 515, or 520(m) of the FDC Act (e.g., an x-ray device, a genetic test, or a surgical instrument)." (81 FR 65040)

In addition, the Final Rule preamble explains that when considering whether a clinical trial "studies" a device product, the 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). (81 FR 65040) If either (a) or (b) are true, this would support that the clinical trial "studies" the device product.

Example: A clinical trial that assesses the safety or efficacy of different radiation doses emitted from a device product previously approved or cleared by the U.S. FDA under

section 510(k), 515, or 520(m) of the FD&C Act would be considered to "study" that radiation-emitting device product under 42 CFR 11.22(b)(1)(ii)(C). For such a study, the responsible party would list "Yes" for the Studies a U.S. FDA-regulated Device Product data element. The trial would be an "applicable device clinical trial," so long as it is interventional, the primary purpose is not a feasibility study, and it also meets one or more of the following conditions: (1) at least one study facility is located in the U.S. (or a U.S. territory); (2) the study is conducted under a U.S. Investigational Device Exemption (IDE); or (3) the device product is manufactured in and exported from the U.S. (or a U.S. territory).

For additional information, see also:

- National Institutes of Health (NIH): Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (PDF) (June 2018)

- FAQ: How do I know if my clinical trial "Studies a U.S. FDA-regulated Drug Product" or "Studies a U.S. FDA-regulated Device Product" when evaluating whether it is an applicable clinical trial (ACT) subject to the regulation under the conditions specified in 42 CFR 11.22(b)? Specifically, for a trial conducted entirely outside the U.S.?

- U.S. Food and Drug Administration (FDA): Premarket Approval (PMA) information

- U.S. FDA: Guidance for Industry and FDA Staff - Humanitarian Use Device (HUD) Designations

- U.S. FDA: Humanitarian Device Exemption: Questions and Answers - Guidance

For additional information about how FDA regulates radiation-emitting products, see also:

- U.S. FDA: Radiation-Emitting Products and Procedures

- U.S. FDA: Radiation-Emitting Products Industry Assistance: Walk-through

- U.S. FDA: How to Study and Market Your Device

Are studies of Class I, II, and III devices required to be registered and submit results?

The regulations in 42 CFR 11.22 require registration for applicable device clinical trials that were initiated after September 27, 2007. For those applicable device clinical trials that were initiated on or after January 18, 2017 that meet the conditions specified in 42 CFR 11.22(b)(1), the regulation requires the submission of registration information listed

in 42 CFR 11.28(a)(2) for clinical trials and in 42 CFR 11.28(b) for pediatric postmarket surveillance of a device product that is not a clinical trial. 42 CFR 11.22(b)(1) describes the conditions for determining whether a clinical trial or study initiated on or after January 18, 2017 is an "applicable clinical device trial." 42 CFR 11.10(a) explains that an applicable device clinical trial studies a device product "subject to section 510(k), 515, or 520(m) of the [FD&C Act]." The Final Rule preamble further clarifies that 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) permitting the device product to be marketed, (2) an order under section 515 of the FD&C Act approving a pre-market approval application for the device product, or (3) an HDE [or Humanitarian Device Exemption] under section 520(m) of the FD&C Act." (81 FR 65012)

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.

For additional information, see also:

- U.S. Food and Drug Administration (FDA): Classify your medical device
- U.S. FDA: Glossary of the Guidance for Industry and Staff: In-Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions (PDF) (June 2010) (includes relevant definitions, e.g., Class I, II, and III devices)

- FAQ: How do I know if my clinical trial "Studies a U.S. FDA-regulated Drug Product" or "Studies a U.S. FDA-regulated Device Product" when evaluating whether it is an applicable clinical trial (ACT) subject to the regulation under the conditions specified in 42 CFR 11.22(b)? Specifically, for a trial conducted entirely outside the U.S.?

Is a study coordinating center located in the United States considered to be a "Facility Location" within the United States for evaluating whether a study is an applicable clinical trial?

A clinical trial enrolling participants only at locations outside the United States, but using a study coordinating center in the United States (with no participants enrolled at the coordinating center location itself), would not be considered to have a "Facility Location" in the United States.

The criteria for a study initiated on or after January 18, 2017, to be an applicable clinical trial (ACT) are specified in 42 CFR 11.22(b). One of these criteria is met if the clinical trial has "at least one Facility Location … within the United States or one of its territories" (42 CFR 11.22(b)(1)(ii)(D)(1) and 42 CFR 11.22(b)(2)(iv)(A)). Facility Location, a component of the Facility Information data element (see 42 CFR 11.28(a)(2)(iii)(C)), is addressed in 42 CFR 11.10(b)(31)(ii). It refers to the city, state, country, and Zip Code (for U.S. locations, including territories of the U.S.) for each "participating facility" in a clinical trial. Whether a site is considered a "participating facility" is dependent on whether participants can enroll at that site; this is reflected in 42 CFR 11.10(b)(31)(iii)(A), which describes Facility Contact Information in reference to enrollment at that particular site. A study coordinating center that may provide study oversight or data management and analysis support, but that does not enroll participants at that location, would not be considered a "participating facility" as described in Facility Location. Therefore, the coordinating center would not be considered a Facility Location for the purposes of 42 CFR 11.28(a)(2)(iii)(C) and the ACT criteria outlined in 42 CFR 11.22(b).

Are "pilot" drug or device studies considered to be an "applicable drug clinical trial" or "applicable device clinical trial," respectively, under the regulation?

It depends. The terms "pilot" drug or device study are not interchangeable with the terms "phase 1" drug study or "feasibility" device study, respectively. The regulation does not identify "pilot" studies in defining "applicable drug clinical trial" and "applicable device clinical trial" in 42 CFR 11.10(a) and 42 CFR 11.22(b). Therefore, the characteristics of each individual clinical trial of a drug, biological, or device product must be evaluated to determine whether it meets the applicable clinical trial definition, independent of whether the responsible party considers the trial to be a "pilot" study. We note that the definition of applicable drug clinical trial in 42 CFR 11.10(a) excludes phase 1 clinical investigations and the definition of applicable device clinical trial excludes certain types of small clinical trials to determine the feasibility of a device product.

The regulation states that phase 1 has the meaning given in 21 CFR 312.21. In summary, a phase 1 trial includes the initial introduction of an investigational new drug into humans and is 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. Phase 1 trials 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. We note that these provisions in the regulation do not use the term "pilot."

Similarly, the definition of "applicable device clinical trial" in 42 CFR 11.10(a) excludes "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." The provision does not use the term "pilot." However, the Final Rule preamble does explain that feasibility studies are sometimes referred to as phase 1 studies, pilot studies, prototype studies, or introductory trials and notes that use of these terms does not necessarily mean that the study is a feasibility study under the definition. (81 FR 65011)

The Final Rule preamble also explains that the phrase "feasibility study" is consistent with FDA's description of an "early feasibility study" and "traditional feasibility study," in FDA's guidance Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies (October 2013). (81 FR 65011) The Final Rule preamble explains that it is likely that only early feasibility studies, and not traditional feasibility studies, would fall within this exclusion under the 42 CFR 11.10 definition of an "applicable device clinical trial." (81 FR 65011) The Final Rule preamble also clarifies that 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 this exclusion. (81 FR 65011)

For additional information, see also:

- National Institutes of Health (NIH): Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) (PDF) (June 2018)

- FAQ: How do I determine if my study is an applicable clinical trial?

- U.S. Food and Drug Administration (FDA): Guidance for Industry and Food and Drug Administration Staff - Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

Responsible Party

How do I determine who is the responsible party for a study?

The regulations at 42 CFR 11.4(c) outline procedures for determining the responsible party for an applicable clinical trial (ACT) or a clinical trial voluntarily submitted under 42 CFR 11.60. The regulations specify that the sponsor of the trial will be considered the responsible party unless and until a principal investigator has been designated the responsible party in accordance with 42 CFR 11.4(c)(2).

For purposes of the regulation, if an ACT or clinical trial is being conducted under an investigational new drug application (IND) or investigational device exemption (IDE), the IND/IDE holder is considered to be the individual or entity who initiated the ACT or clinical trial and, therefore, the sponsor as defined in 42 CFR 11.10(a), regardless of how the clinical trial is being funded.

For clinical trials not conducted under an IND or IDE, the sponsor is considered to be the person or entity who initiated the trial and would be identified as follows:

1. Where the clinical trial is being conducted by an entity under a research assistance funding agreement such as a grant or sponsored research agreement, the funding recipient generally is considered to be the initiator of the clinical trial, and therefore, the sponsor. This is because, as a general rule, when a clinical trial is funded in this manner, the funding recipient "initiates" the clinical trial process by, for example, submitting a funding proposal and designing the clinical trial.

2. Where the clinical trial is being conducted by an entity under a procurement funding agreement such as a contract, the party obtaining the goods or services for its direct benefit or use (the funder) generally is considered to be the initiator of the trial, and therefore, the sponsor. This is because, as a general rule, when a clinical trial is funded in this manner, it is the funder of the clinical trial that initiates the clinical trial process by, for example, contracting with another entity for that entity to conduct a clinical trial meeting the specifications of the funder.

3. Where there is no funding agreement supporting the clinical trial, the person or entity who initiated the clinical trial by preparing and/or planning the clinical trial, and who has appropriate authority and control over the clinical trial to carry out the responsibilities under section 402(j) of the Public Health Service Act (including this part) is the sponsor. [81 FR 65003-04]

Can the sponsor designate a principal investigator as the responsible party?
Yes. The sponsor of the clinical trial, whether an individual or entity, is the responsible party, unless the principal investigator has been designated the responsible party in accordance with 42 CFR 11.4(c)(2). The principal investigator may be designated by a sponsor, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the

results of the trial, and has the ability to meet all of the requirements under the regulation for submitting and updating of clinical trial information. If the principal investigator does not meet the specified conditions for serving as the responsible party, the sponsor cannot designate the principal investigator as the responsible party, and the sponsor must remain the responsible party.

The format for designation of the principal investigator as the responsible party by the sponsor is specified in ClinicalTrials.gov by having the principal investigator submit clinical trial information via the sponsor's Protocol Registration and Results System (PRS) organizational account (the sponsor must provide an account for the principal investigator within the sponsor's PRS organizational account). The acknowledgement is reflected by having the principal investigator list their name as the responsible party and indicate that they were designated as the responsible party by the sponsor.
If and when a designated principal investigator no longer meets or is no longer able to meet all of the requirements of a responsible party, 42 CFR 11.4(c)(3) outlines the mechanisms by which, if the withdrawal of such designation occurs, the sponsor would become the responsible party. This might occur if, for example, a principal investigator dies, retires, changes jobs, or turns control of the clinical trial data over to the sponsor.

Who should submit an Expanded Access record?
The final rule clarifies that expanded access (EA) use of a drug, biological, or device product is not considered an "applicable clinical trial" (ACT) under the definition in 42 CFR 11.10 (81 FR 65009-10). Thus, the submission of clinical trial registration and results information for EA use would not be required by 42 CFR 11.22 and 42 CFR 11.42.

However, for "applicable drug clinical trials" that are required to submit the registration information specified in 42 CFR 11.28, and the responsible party is both the drug manufacturer and trial sponsor, information on the availability of investigational drug products for expanded access is required to be submitted as part of the registration information under 42 CFR 11.28(a)(2)(ii)(H). In addition, an expanded access record must be submitted as required under 42 CFR 11.28(c) to provide details about how to obtain access to the investigational drug (including biological) product. The regulations at 42 CFR 11.64(a)(1)(ii)(D) and (E) requires this availability of expanded access and expanded access record information to be updated. More information about the expanded access submission requirements is available in the final rule preamble. (81 FR 65059-62)

Who is the responsible party for a pediatric postmarket surveillance of a device product that is not a clinical trial?
For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party would be considered the entity FDA, under section 522 of the FD&C

Act, orders to conduct the pediatric postmarket surveillance of a device product. [42 CFR 11.4(c), 11.10(a); 81 FR 65003]

Registration Information and Submission Deadlines

If my study is an applicable clinical trial (ACT), am I required to register?
The regulations at 42 CFR 11.22(a) require the registration of any ACT that is (1) initiated after September 27, 2007, or (2) initiated on or before September 27, 2007 and is ongoing (i.e., not yet reached the Primary Completion Date) on December 26, 2007.

What registration information must I submit if my applicable clinical trial is required to be registered?
The regulations at 42 CFR 11.28 address which registration information requirements apply to which studies. The "Applicability of Requirements in 42 CFR Part 11" table may be used to evaluate whether the registration information requirements in 42 CFR Part 11 or section 402(j) of the Public Health Service (PHS) Act apply to specific studies. (81 FR 65121)

As outlined in the table, required registration information is determined by the study initiation date. The initiation date is the date on which the trial is initiated (i.e., the actual Study Start Date as defined in 42 CFR 11.10(b)(16). (81 FR 65120):

- Study Start Date on or before September 27, 2007, and ongoing on December 26, 2007: Follow requirements in section 402(j)(2)(A)(ii) of the PHS Act.

- Study Start Date after September 27, 2007 but before January 18, 2017: Follow requirements in section 402(j)(2)(A)(ii) of the PHS Act.

- Study Start Date on or after January 18, 2017: Follow requirements specified in 42 CFR 11.28 of the final rule.

When must I submit the required clinical trial registration information?
The regulations at 42 CFR 11.24(a) require that, for an applicable clinical trial for which registration information is required to be submitted, the registration information specified in section 402(j)(2)(A)(ii) of the PHS Act or 42 CFR 11.28(a) must be submitted within 21 days after the first human subject is enrolled. The final rule in 42 CFR 11.10(a) defines "enroll or enrolled" to mean 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." The definition further states that "for the purposes of … [42 CFR part 11], 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."

For an applicable device clinical trial that is a pediatric postmarket surveillance of a device product and is not a clinical trial, the registration information specified in section 402(j)(2)(A)(ii) of the PHS Act or 42 CFR 11.28(b) must be submitted within 21 days after FDA approves the postmarket surveillance plan.

For additional information, see also:

- FAQ: When must I update clinical trial registration information?

How are examinations by telephone call or other electronic means considered in determining when an applicable clinical trial reaches its "primary completion date" or "study completion date" under the regulation?
The final rule in 42 CFR 11.10(a) defines "[primary] completion date" for a clinical trial as the "date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated…. The final rule in 42 CFR 11.10(a) also defines "study completion date" for a clinical trial as the "date the final subject was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (e.g., last subject's last visit), whether the clinical trial concluded according to the pre-specified protocol or was terminated…." The final rule preamble addresses these definitions in greater detail in Section IV.A.5. §11.10 – "What definitions apply to this part?" (81 FR 65008) The examination of a subject or administration of an intervention for purposes of "final collection of data" can include a broad range of methods of examination, including physical examination or examination by telephone or other electronic means.

At what point is a human subject considered to be "enrolled" in an applicable clinical trial?
"Enrolled" is defined in 42 CFR 11.10(a) as 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. The regulation explains that, for the purposes of this part, 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.

The Enrollment data element is defined in 42 CFR 11.10(b)(18) as the estimated total number of human subjects to be enrolled (target number) or the actual total number of human subjects that are enrolled in the clinical trial. That regulation further explains that once the trial has reached the primary completion date, the responsible party must update the Enrollment data element to reflect the actual number of human subjects enrolled in the clinical trial.

The Final Rule preamble (81 FR 65022) provides additional clarification of the "enroll or enrolled" definition in 42 CFR 11.10(a) by addressing two scenarios involving signing of the informed consent document. The first scenario involves the use of a separate informed consent document for screening. In this situation, there are two distinct informed consent documents: one for trial screening (for eligibility) and if eligible, one for trial participation. Under this first scenario, the signing of the second separate informed consent document for trial participation would mean the subject is enrolled in the clinical trial.

In the second scenario, there is only one informed consent document for both trial screening and trial participation. In this scenario, the Final Rule preamble explains that a participant would not be considered enrolled until he or she met all the eligibility criteria assessed during screening, unless the participant is considered enrolled as outlined specifically in the protocol. (81 FR 65022) The Final Rule preamble further explains that when there is only one informed consent document for both trial screening and trial participation, registration information must be submitted as described in 42 CFR 11.24 no later than 21 calendar days after the first participant signs the informed consent form and begins trial participation, in accordance with the protocol.
Based on this clarification, when there is only one informed consent document for both trial screening and trial participation, whether a human subject "participates" in a study, and is therefore considered "enrolled" under the definition in 42 CFR 11.10(a), is determined by the protocol. This determination may vary across clinical trial protocols. For example, assignment to a study arm may be considered the beginning of trial participation based on a particular study protocol. In this example, if the study was halted prematurely before any subjects were assigned to a study arm (i.e., the Overall Recruitment Status is "Withdrawn"), none of the subjects would be considered enrolled, even though they had already signed the informed consent document. Also, if a human subject signs the informed consent document but then withdraws his or her informed consent before participation begins, the subject would not be considered "enrolled" in the clinical trial under the definition.

We also note that the definition of "enrolled" is important for determining the Study Start Date. Study Start Date is defined in 42 CFR 11.10(b)(16) as the estimated date on which the clinical trial will be open for recruitment of human subjects, or the actual date on which the first human subject was enrolled.

What is the Primary Completion Date and/or Study Completion Date when an outcome is measured or assessed after a study participant has been examined or received an intervention for that outcome?
The Primary Completion Date is the date that the final study participant was examined or received an intervention for the purpose of the final collection of data for the primary outcome. Similarly, the Study Completion Date is the date that the final study participant was examined or received an intervention for the purpose of the final collection of data

for the primary and secondary outcome measures and adverse events (see the definitions in 42 CFR 11.10(a)).

The date that the final study participant was examined or received an intervention for the purpose of the final collection of data is the date of the examination or the administration of the intervention itself, not the date of any later assessment, analysis, or interpretation of the collected outcome or adverse event data. For example, if a participant was examined with a magnetic resonance imaging (MRI) scan for the primary outcome, the Primary Completion Date is the date that the last participant underwent the MRI, and not when the MRI was subsequently assessed using a central reading process or other review procedure. More information on this point is available in the Final Rule preamble. (81 FR 65019-20)

Results Information and Submission Deadlines

Am I required to submit results information for my applicable clinical trial (ACT)?
The regulations at 42 CFR 11.42 address those applicable clinical trials for which a responsible party must submit results information. Whether the results information requirements in 42 CFR Part 11 or section 402(j) of the Public Health Service (PHS) Act apply to specific applicable clinical trials is determined by the Primary Completion Date.

- For ACTs that were required to be registered and with a Primary Completion Date before January 18, 2017:
    - If the ACT studied a drug, biological, or device product that was approved, licensed or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. (42 CFR 11.42(a)(1)).
    - If the ACT studied a drug, biological, or device product that was not approved, licensed, or cleared for any use as of the Primary Completion Date but is subsequently approved, licensed, or cleared, then the responsible party is required to submit the results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act not later than 30 days *after* the product is approved, licensed, or cleared by the Food and Drug Administration, in accordance with section 402(j)(3)(E)(iv) of the PHS Act and pursuant to the Federal Court decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020).
- For ACTs that are required to be registered and with a Primary Completion Date on or after January 18, 2017:

- If the ACT studies a drug, biological, or device product that is approved, licensed or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information specified in 42 CFR 11.48. (42 CFR 11.42(a)(2)).

- If the ACT studies a drug, biological, or device product that is not approved, licensed, or cleared as of the Primary Completion Date, then the responsible party is required to submit the results information specified in 42 CFR 11.48. (42 CFR 11.42(b)).

The regulation at 42 CFR 11.60 also establishes requirements for the voluntary submission of results information that are not otherwise required to be submitted under 42 CFR 11.42.

Am I required to submit results information for my applicable clinical trial (ACT) if the primary completion date was before January 18, 2017 (the effective date of the Final Rule)? If so, when?

Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801) requires submission of results information for applicable clinical trials (ACTs) that were initiated after September 27, 2007, or that were ongoing as of December 26, 2007, if the product studied in the ACT is approved, licensed, or cleared by the Food and Drug Administration (FDA) at any time, including after the ACT's primary completion date. For ACTs subject to FDAAA's registration and results submission requirements that have a primary completion date before January 18, 2017 (the effective date of the Final Rule), results information must be submitted as follows:

- If the ACT studied a drug, biological, or device product that was approved, licensed, or cleared by FDA *before* the ACT's primary completion date, the responsible party generally must submit the results information specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the Public Health Service (PHS) Act no later than 1 year after the study's primary completion date; however, results information submission for these ACTs may be delayed under certain conditions as specified in section 402(j)(3)(E)(v) (seeking approval, licensing, or clearance of a new use for the drug, biological, or device product) and section 402(j)(3)(E)(vi) (requesting an extension for good cause) of the PHS Act.

- Pursuant to the Federal Court decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020), if the ACT studied a drug, biological, or device product that was not approved, licensed, or cleared for any use as of the primary completion date but is subsequently approved, licensed, or cleared by FDA *on or after* the ACT's primary completion date, the responsible party must submit the results information specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act within 30 days after approval, licensure, or clearance of the drug, biological, or device product, in accordance with section 402(j)(3)(E)(iv) of the PHS Act (seeking initial approval, licensure, or clearance of the drug, biological,

or device product) and may be delayed under certain conditions as specified in section 402(j)(3)(E)(vi) (requesting an extension for good cause) of the PHS Act.

If the results submission deadline has already passed for an ACT affected by the Federal Court decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020), what is the deadline for submitting results information?
Responsible parties for such ACTs should submit the results information specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act as soon as possible.

What are the potential consequences of not submitting required results information for ACTs affected by the Federal Court's decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020)?
The National Institutes of Health (NIH) and Food and Drug Administration (FDA) encourage responsible parties to submit required results information for ACTs affected by the Federal Court's decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020) as soon as possible. FDA and NIH may take action against responsible parties if they do not submit required results information for ACTs affected by the Federal Court's decision. Failure to submit required results information is a prohibited act under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(jj)(2), for which FDA could pursue civil monetary penalties under 21 U.S.C. 333(f)(3) against the ACT's responsible party. For an ACT for which an NIH or FDA grantee is the responsible party, failure to submit required results information could result in NIH or FDA, as applicable, not releasing remaining funding for a grant or funding for a future grant in accordance with section 402(j)(5)(A) of the PHS Act.

When is required clinical trial results information due?
For applicable clinical trials that are subject to 42 CFR 11.42, the standard submission deadline for results information is no later than 1 year after the study's Primary Completion Date, as described in 42 CFR 11.44(a) of the final rule.

For ACTs with a primary completion date on or after January 18, 2017, the regulations provide for the delayed submission of results information under certain conditions with certification if the responsible party is seeking approval, licensure, or clearance of a new use being studied for a product that previously was approved, licensed, or cleared by FDA (42 CFR 11.44(b)). For ACTs with a primary completion date on or after January 18, 2017, the regulations also provide for the delayed submission of results information under certain conditions with certification if the responsible party is seeking initial approval, licensure, or clearance for the studied product (42 CFR 11.44(c)). Both 42 CFR 11.44(b) and 42 CFR 11.44(c) require that the responsible party submit the certification prior to the date of (i.e., the day before) the standard submission deadline for results information. The standard submission deadline for results information is no later than 1 year after the ACT's primary completion date.

The deadline for the delayed submission of results information as specified in 42 CFR 11.44(b) or 42 CFR 11.44(c) is 30 calendar days after the earliest of specific events described in each provision, with a maximum deadline for delayed results information submission of 2 years after the date the certification was submitted. Specific deadlines are also described in 42 CFR 11.44(d) for the submission of partial results information. An extension for good cause may be requested under conditions specified in 42 CFR 11.44(e). The preamble of the final rule explains that such requests will be granted in limited circumstances. (81 FR 65076-79)
For additional information, see also:

- FAQ: Am I required to submit results information for my applicable clinical trial (ACT) if the primary completion date was before January 18, 2017 (the effective date of the Final Rule)? If so, when?

- FAQ: What is the deadline for submitting a certification for delayed submission of results information?

What is the deadline for submitting a certification for delayed submission of results information?
The regulations at 42 CFR 11.44(b) and 42 CFR 11.44(c) address the circumstances under which a responsible party may submit a certification for delayed submission of results information ("certification for delay") for an applicable clinical trial (ACT) with a primary completion date on or after January 18, 2017. Both 42 CFR 11.44(b) and 42 CFR 11.44(c) require that the responsible party submit the certification prior to the date of (i.e., the day before) the standard submission deadline for results information specified in 42 CFR 11.44(a). The standard submission deadline for results information is no later than 1 year after the primary completion date. A certification for delay for an ACT with a primary completion date on or after January 18, 2017, is considered late if it is submitted on or after the date of the standard submission deadline for results information.

Responsible parties submit certifications for delay via the ClinicalTrials.gov Protocol Registration and Results System (PRS). After National Library of Medicine (NLM) staff process the certification for posting, the PRS automatically assigns the ACT's Results Expected date to be a maximum of 2 years after the date that the certification for delay was submitted.

As of February 1, 2021, the PRS no longer permits responsible parties to submit late certifications for delay for ACTs with a primary completion date on or after January 18, 2017. This change aligns the PRS's automated validation rules for certifications for delay with the regulatory requirements in 42 CFR 11.44(b) and 42 CFR 11.44(c). Similarly, as of February 1, 2021, responsible parties may not submit "certify new use" certifications for ACTs with a primary completion date before January 18, 2017.

Prior to February 1, 2021, a responsible party may have submitted a late certification for delay. If this occurred, the responsible party should submit results information as soon as possible but no later than the following dates:

- 30 calendar days after the earliest of the events described in 42 CFR 11.44(b)(1)(i)-(iii) or 42 CFR 11.44(c)(1)(i)-(ii), as applicable; or

- 2 years after the date that the certification was submitted (i.e., the Results Expected date assigned to the ACT in the PRS) if none of the events described in 42 CFR 11.44(b)(1)(i)-(iii) or 42 CFR 11.44(c)(1)(i)-(ii), as applicable, has occurred by that date.

Failure to submit required results information is a prohibited act under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(jj)(2), for which FDA could pursue civil monetary penalties under 21 U.S.C. 333(f)(3) against the ACT's responsible party. For an ACT for which an NIH or FDA recipient is the responsible party, failure to submit required results information could result in NIH or FDA, as applicable, not releasing remaining funding for a grant or funding for a future grant, pursuant to section 402(j)(5)(A) of the Public Health Service Act.

For additional information, see also:

- FAQ: When is required clinical trial results information due?

- FAQ: To which trials do the potential legal consequences described in 42 CFR 11.66 apply?

What is the results information submission deadline for applicable clinical trials (ACTs) of drug, biological, or device products that are not approved, licensed, or cleared for any use and studied in conjunction with, or in comparison to, approved, licensed, or cleared products?
The clinical trial results information submission deadlines for ACTs that fall within the scope of 42 CFR 11.42 are set out in 42 CFR 11.44. The standard submission deadline for results information is no later than 1 year after the study's primary completion date. (42 CFR 11.44(a)) However, an ACT with a primary completion date on or after January 18, 2017, would be eligible for delayed submission of results if, prior to the date of (i.e., the day before) the standard submission deadline for results information, the responsible party certifies that the ACT studies a Food and Drug Administration (FDA)-regulated drug product (including a biological product) or device product that was not approved, licensed, or cleared by FDA for any use before the primary completion date, and that the sponsor intends to continue with product development and is either seeking, or may at a future date seek, FDA approval, licensure, or clearance of the product under study. (42 CFR 11.44(c)) Section 11.44(c) applies when a drug product

(including a biological product) or device product being studied is not approved, licensed, or cleared by FDA for any use. The fact that the unapproved, unlicensed, or uncleared product is being studied in conjunction with or in comparison to an approved, licensed, or cleared product does not nullify the trial's eligibility for the delayed submission of results provision under 42 CFR 11.44(c). In addition, this fact does not require the products being used in conjunction with each other to be considered an approved, licensed, or cleared product, or to be a new use of a previously approved, licensed, or cleared product.

For more information on the results information submission requirements, see also:

- FAQ: Am I required to submit results information for my applicable clinical trial (ACT) if the primary completion date was before January 18, 2017 (the effective date of the Final Rule)? If so, when?

- FAQ: Am I required to submit results information for my applicable clinical trial (ACT)?

- FAQ: When is required clinical trial results information due?

How are "approval, licensure, or clearance of a new use" and "initial approval, licensure, or clearance" defined for the purposes of determining if a study may qualify for delayed submission of results information with certification?
The regulations at 42 CFR 11.44(b) and 11.44(c) provide for the delayed submission of results information for an applicable clinical trial (ACT) with certification under certain conditions. Under 42 CFR 11.44(c), results information submission may be delayed if, prior to the date of (i.e., the day before) the standard submission deadline for results information specified in 42 CFR 11.44(a), the responsible party of an ACT certifies that a studied FDA-regulated drug, biological, or device product was not approved, licensed, or cleared by FDA for any use before the primary completion date of the trial. The responsible party of such an ACT must also certify that the sponsor of the ACT intends to continue with product development and is seeking, or may seek at a future date, initial approval, licensure, or clearance by the FDA for the studied product. Under 42 CFR 11.44(b) results information submission may be delayed if the responsible party certifies that the ACT sponsor, who is also the manufacturer of the FDA-regulated product, is seeking approval, licensure, or clearance of the new use being studied in that ACT for a product that previously has been approved, licensed, or cleared by the FDA and has filed or will file within 1 year an application or premarket notification for the new use being studied. A new use is one which is not included in the labeling of the approved, licensed, or cleared drug, biological, or device product.

The Final Rule preamble clarified that "drug product" and "biological product" refer to a finished product that is approved or licensed for marketing, and not to the active

ingredients or active moiety in such a product. (81 FR 65070) Thus, "initial approval" (or "initial licensure") in 42 CFR 11.44(c) pertains to the approval or licensure of an original New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA), whereas "new use" in 42 CFR 11.44(b) pertains to the approval or licensure of a supplemental NDA, ANDA, or BLA for an additional use for that particular drug product or biological product. (81 FR 65070)

Similarly, "device product" refers to a manufacturer's particular "product" rather than a general "type" of device. (81 FR 65073) Thus, "initial approval" of a device product under sections 515 or 520(m) of the Federal Food, Drug, and Cosmetic (FD&C) Act pertains to the approval of an original Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) (81 FR 65070) while "initial clearance" pertains to the clearance of a manufacturer's original 510(k) submission for a particular device product. (81 FR 65071) Whereas "approval of a new use" pertains to the approval of a supplemental PMA under section 515 of the FD&C Act for an additional use for a particular device product (81 FR 65070), "clearance of a new use" pertains to the clearance of the same manufacturer's subsequent 510(k) submission for an additional use for the same device product. (81 FR 65071)

If an ACT studies an FDA-regulated device product that has not been previously approved or cleared (does not have "initial approval" or "initial clearance") by the U.S. FDA for one or more uses, then the responsible party is required to answer "Yes" to the Device Product Not Approved or Cleared by U.S. FDA data element under 42 CFR 11.28(a)(2)(i)(P). The Final Rule preamble also explains for this data element that "if a manufacturer's original 510(k) submission for its particular device product has not been previously cleared, then that manufacturer's device product would be considered a 'device product not cleared by FDA,' even if another manufacturer has already obtained 510(k) clearance of its device product within the same product type." (81 FR 65042) The responsible party is required to update this data element under 42 CFR 11.64(a)(1)(ii)(M) within 15 calendar days after a change in approval or clearance status has occurred.

Also note that clinical trial registration information submitted for an ACT of a device product that has not been previously approved or cleared (does not have "initial approval" or "initial clearance") is subject to the delayed posting provision at 42 CFR 11.35(b)(2)(i), which states that applicable device clinical trial registration information for a device product that has not been previously approved or cleared will be publicly posted not earlier than the date of FDA approval or clearance. The responsible party for the ACT may authorize public posting of the information prior to the date of FDA approval or clearance of its device product as specified at 42 CFR 11.35(b)(2)(ii) by answering "Yes" to the Post Prior to U.S. FDA Approval or Clearance data element under 42 CFR 11.28(a)(2)(i)(Q).
For more information, see also:

- FAQ: Am I required to submit results information for my applicable clinical trial (ACT)?

For an applicable clinical trial (ACT) for which results information must be submitted under 42 CFR 11.42, if a certification of delay for an unapproved product ("certify initial approval") has been submitted under 42 CFR 11.44(c) and the sponsor later decides to discontinue development of the product, when are results due?

Under 42 CFR 11.44(c), a responsible party may submit a certification ("certify initial approval") prior to the date of (i.e., the day before) the standard submission deadline for results information specified in 42 CFR 11.44(a) to indicate that an ACT studies an FDA-regulated drug, biological, or device product that was not approved, licensed, or cleared by FDA for any use before the trial's primary completion date, and that the sponsor intends to continue with product development and is either seeking, or may at a future date seek, FDA approval, licensure, or clearance of the studied product. In this case, the deadline for results information submission is 30 days after the earlier of:

- FDA approval, licensure, or clearance of the product for any use that is studied in the ACT, or

- The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days

The regulation also states in 42 CFR 11.44(c) that the maximum deadline for results information submission is 2 years after the date on which the certification was submitted, except to the extent that 42 CFR 11.44(d), which pertains to the submission of partial results information, applies.

As explained in the Final Rule preamble, certifications for delayed results information submission cannot be submitted for ACTs of products that the sponsor has no intention of marketing or for which product development has been abandoned. (81 FR 65073) In these situations the criteria at 42 CFR 11.44(c) would not be met.

For a study that is required to submit results under 42 CFR 11.42 and a certification of delay for an unapproved, unlicensed, or uncleared product ("certify initial approval") has been submitted under 42 CFR 11.44(c), but the sponsor later decides to discontinue development of the product, then results information is still required according to the above-described deadlines in the regulation (i.e., no later than 2 years after the date on which the certification was submitted). Should the decision to discontinue the development of the product occur before these deadlines, we encourage the responsible party to submit clinical trial results information as soon as possible after deciding to discontinue product development.

When are results due for an applicable clinical trial (ACT), if a certification of delay for an approved, licensed, or cleared product ("certify new use") has been submitted under 42 CFR 11.44(b)?

Under 42 CFR 11.44(b), results information submission may be delayed if the responsible party submits a certification prior to the date of (i.e., the day before) standard submission deadline for results information specified in 42 CFR 11.44(a) indicating that the ACT studies a new use of an FDA-approved drug, biological, or device product (that is, a use not included in the labeling), and the manufacturer of the drug, biological, or device product is the sponsor of the trial and has filed or will file within 1 year of the certification submission date an application to FDA for approval or clearance of that use (referred to on ClinicalTrials.gov as "certify new use").
In this case, the deadline for results information submission is 30 days after the earlier of:

- FDA approval, licensure, or clearance of the product for any use that is studied in the ACT
- FDA issuing a letter that ends the regulatory review cycle for the application or submission but does not approve, license, or clear the product, or
- The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days

If none of the above events occurs, then the maximum deadline for results information submission is 2 years after the date on which the certification was submitted, except to the extent that 42 CFR 11.44(d), which pertains to the submission of partial results information, applies.

If the sponsor does not file the marketing application or pre-market notification with FDA within 1 year of the certification submission date, we encourage the responsible party to submit required results information no later than 1 year after the certification submission date. Should the sponsor decide sooner than 1 year after the certification submission date that it will not file the marketing application or pre-market notification, we encourage the responsible party to submit clinical trial results information as soon as possible after making this decision.

For additional information, see also:

- FAQ: When is required clinical trial results information due?
- FAQ: How are "approval, licensure, or clearance of a new use" and "initial approval, licensure, or clearance" defined for the purposes of determining if a study may qualify for delayed submission of results information with certification?

Study Documents

Is a protocol and statistical analysis plan (SAP) required to be submitted?
The regulations at 42 CFR 11.48(a)(5) require a copy of the protocol and SAP (if not included in the protocol) to be submitted as part of clinical trial results information for those applicable clinical trials with a Primary Completion Date on or after January 18, 2017. The submission of a protocol and SAP is not required for those applicable clinical trials with a Primary Completion Date before January 18, 2017.

The regulations at 42 CFR 11.48(a)(5) also state that a "responsible party may redact names, addresses, and other personally identifiable information, as well as any trade secret and/or confidential commercial information (as those terms are defined in the Freedom of Information Act (5 U.S.C. 552) and the Trade Secrets Act (18 U.S.C. 1905)) contained in the protocol or statistical analysis plan prior to submission, unless such information is otherwise required to be submitted under this part."

Additional information about redaction of protocols is also provided in the preamble to 42 CFR part 11. (81 FR 64999 - 65002) This information includes noting that "[m]ore specific guidance regarding redaction will be considered in the future" and that the "protocol and statistical analysis plan must be submitted in a common electronic document format specified at https://prsinfo.clinicaltrials.gov."

The protocol and, if separate, the SAP are to be posted with other clinical trial results, in accordance with 42 CFR 11.52. (81 FR 65002)

Are appendices required to be included in the uploaded study protocol?
The regulation in 42 CFR 11.48(a)(5) requires the responsible party to submit with results information "a copy of the protocol and statistical analysis plan (if not included in the protocol), including all amendments that have been approved by a human subjects protection review board (if applicable) before the time of submission … and that apply to all clinical trial Facility Locations." The regulation in 42 CFR 11.10(a) defines "protocol" as "the written description of the clinical trial, including objective(s), design, and methods. It may also include relevant scientific background and statistical considerations." The Final Rule preamble explains that the regulation requires submission of the full version of the protocol. (81 FR 65001) The Final Rule preamble also explains that "protocols provide information in a context that is not captured by [data] elements alone and that the protocols will improve transparency and the quality of reporting by providing a more complete picture of the trial." (81 FR 65000)

We consider protocol appendices that contain a "description of the clinical trial, including objective(s), design, and methods," and any "relevant scientific background and statistical considerations," to be part of the full protocol and as such they must be included with the uploaded protocol. We note that before including any appendices with

the study protocol for posting, responsible parties may redact information in a protocol appendix consistent with 42 CFR 11.48(a)(5), which permits the responsible party to redact, among other things, trade secret and/or confidential commercial information from the protocol and statistical analysis plan prior to submission, unless such information is otherwise required to be submitted by the regulation.

For more information on the protocol submission requirements, see also:

- FAQ: Is a protocol and statistical analysis plan (SAP) required to be submitted?

Updates to Clinical Trial Information

When must I update clinical trial registration information?
For clinical trials initiated on or after January 18, 2017, the regulations at 42 CFR 11.64(a)(1)(ii) specify update requirements. In general, clinical trial registration information submitted to ClinicalTrials.gov must be updated not less than once every 12 months. The regulations further require that some data elements be updated more rapidly, as summarized in the Table below. In addition, if a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial, the regulations require that updates to any relevant clinical trial information be submitted not later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board. See the Final Rule preamble (81 FR 65109-17) and the regulations at 42 CFR 11.64 for a more complete elaboration and specification of these requirements.

Table. Clinical Trial Registration Data Elements for More Frequent Updating

Data Element	Deadline for Updating (i.e., not later than the specified date)
Study Start Date	30 calendar days after the first subject is enrolled (if the first human subject was not enrolled at the time of registration).
Intervention Name(s)	30 calendar days after a nonproprietary name is established.
Availability of Expanded Access	30 calendar days after expanded access becomes available (if available after registration); and 30 calendar days after an NCT number is assigned to a newly created expanded access record. [1]
Expanded Access Status	30 calendar days after a change in the availability of expanded access.
Expanded Access Type	30 calendar days after a change in the type(s) of available expanded access.

Overall Recruitment Status	30 calendar days after a change in overall recruitment status. [2]
Individual Site Status	30 calendar days after a change in status of any individual site.
Human Subjects Protection Review Board Status	30 calendar days after a change in status.
Primary Completion Date	30 calendar days after the clinical trial reaches its actual primary completion date.
Enrollment	At the time the primary completion date is changed to "actual," the actual number of participants enrolled must be submitted.
Study Completion Date	30 calendar days after the clinical trial reaches its actual study completion date.
Responsible Party, by Official Title	30 calendar days after a change in the responsible party or the official title of the responsible party.
Responsible Party Contact Information	30 calendar days after a change in the responsible party or the contact information for the responsible party.
Device Product Not Approved or Cleared by U.S. FDA	15 calendar days after a change in approval or clearance status has occurred.
Device Product Not Approved or Cleared by U.S. FDA	15 calendar days after a change in approval or clearance status has occurred.
Record Verification Date	Any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.

[1] If expanded access to an investigational drug product becomes available after a clinical trial of that drug product has been registered and an expanded access record has not yet been created, a responsible party who is both the manufacturer of the investigational product and the sponsor of the applicable clinical trial must also, not later than 30 calendar days after expanded access becomes available, submit the data elements in accordance with 42 CFR 11.28(c) to create an expanded access record.

[2] If Overall Recruitment Status is changed to "suspended," "terminated," or "withdrawn," the Why Study Stopped data element must be submitted at the time the update is made.

What are the requirements for updating clinical trial registration information when a Human Subjects Review Board approves a protocol amendment?
The regulation at 42 CFR 11.64(a)(1)(ii)(O)) specifies for applicable clinical trials initiated on or after January 18, 2017, or for which registration information was voluntarily submitted pursuant to 42 CFR 11.60(c), that "[i]f a protocol is amended in such a manner that changes are communicated to human subjects in the clinical trial, updates to any relevant clinical trial registration information data elements must be submitted not later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board." For determining the date by which the information must be updated, the preamble to 42 CFR Part 11 clarified that if there is more than one human subjects protection review board for a multi-site trial, the date of the first board approval for the amendment should be used. (81 FR 65110) This requirement applies to any human subjects protection review board and is not limited to amendments by human subjects protection review boards in the United States. Clinical trial registration information must include information for the entire study, because the entire clinical study is considered to be the applicable device or drug clinical trial. (81 FR 65013, 81 FR 65015)

When does my obligation to update clinical trial information end?
The regulation in 42 CFR 11.64(a)(3) specifies when a responsible party is no longer required to update a clinical trial record. To determine when updates are no longer required under 42 CFR 11.64(a) on a study record for an applicable clinical trial (ACT) that must be registered pursuant to 42 CFR 11.22(a) or for a voluntarily-submitted clinical trial, the type of clinical trial information and the primary completion date must be considered, as summarized below:

- For ACTs that are required by 42 CFR 11.22(a) to be registered and with a primary completion date *on or after* January 18, 2017:
    - The responsible party's obligation to submit updates under 42 CFR 11.64(a) ends when all required clinical trial results information has been submitted as specified in 42 CFR 11.48 and the responsible party has made all corrections and/or addressed all concerns in response to any electronic notice received under 42 CFR 11.64(b)(1).
- For ACTs that are required by 42 CFR 11.22(a) to be registered and with a primary completion date *before* January 18, 2017:
    - If the ACT studies a drug, biological, or device product that is approved, licensed, or cleared as of the primary completion date, then the

responsible party's obligation to submit updates under section 402(j)(4)(C) of the Public Health Service Act (PHS Act) ends when all required clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act.

- If the ACT studies a drug, biological, or device product that is not approved, licensed, or cleared for any use as of the primary completion date, then clinical trial results information must be submitted not later than 30 days after approval, licensure, or clearance of the drug, biological, or device product for any use, in accordance with section 402(j)(3)(E)(iv) of the PHS Act and pursuant to the Federal Court decision in *Seife et al. v. HHS et al.*, 18-cv-11462 (NRB) (S.D.N.Y. Feb. 24, 2020). A responsible party's obligation to submit updates for such ACT under section 402(j)(4)(C) of the PHS Act ends when all required clinical trial results information has been submitted as specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act.

- For clinical trials initiated *on or after* January 18, 2017, for which clinical trial information is submitted voluntarily pursuant to 42 CFR 11.60(c):

  - The responsible party's obligation to submit updates under 42 CFR 11.60(c)(2)(v), 11.64(a)(1)(ii), and 11.64 (a)(2) ends when all required clinical trial results information has been submitted as specified in 42 CFR 11.48(a) and the responsible party has made all corrections and/or addressed all concerns in response to any electronic notice received under 42 CFR 11.64(b)(1).

In order to ensure the quality and usability of information on ClinicalTrials.gov, responsible parties may update any information in their study records that may have changed after their obligation to update has ended. Responsible parties are also required to correct errors that they identify with clinical trial registration and/or results information, as described in and to the extent required by 42 CFR 11.64(b)(2).

Compliance

What is the final rule's effective date and compliance date?
As explained in the final rule preamble in Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in this Part (81 FR 65118-122), the effective date is on January 18, 2017 and the compliance date is on April 18, 2017. Responsible parties have until April 18, 2017, to come into compliance with the requirements of the final rule.

For more information on the final rule implementation, see: https://prsinfo.clinicaltrials.gov.

To which trials do the potential legal consequences described in 42 CFR 11.66 apply?
"Responsible parties" (as defined in 42 CFR 11.10(a)) must comply with the applicable provisions of section 402(j) of the Public Health Service Act (PHS Act) and the applicable regulations in 42 CFR part 11. The statute and regulations set forth the requirements for responsible parties to submit registration and summary results information to the ClinicalTrials.gov data bank for specified "applicable clinical trials" (ACTs) of drug products (including biological products) and device products.

ACTs are described in section 402(j)(1)(A) of the PHS Act and in 42 CFR 11.10(a). Any applicable clinical trial that (1) is initiated after September 27, 2007, or (2) was initiated on or before September 27, 2007, and was ongoing on December 26, 2007, must be registered with the ClinicalTrials.gov data bank (see section 402(j)(2)(C) of the PHS Act and 42 CFR 11.22(a)). For ACTs that are required to be registered, 42 CFR 11.42 describes for which trials results information must be submitted (see 81 FR 65121 for summary table) and whether they must submit the results information specified in sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act or the results information specified in 42 CFR 11.48.

42 CFR 11.66 describes the potential legal consequences for responsible parties if they do not comply with the requirements to submit registration and results information on applicable clinical trials. Such potential legal consequences include civil or criminal judicial actions, civil monetary penalty actions, and grant funding actions.

For additional information, see:

- U.S. Food and Drug Administration (FDA): Guidance for Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank (August 2020)

Voluntary Submissions

What types of clinical trials are considered voluntary submissions subject to the regulation?
The regulations in 42 CFR 11.60 identify two types of clinical trials for which the submission of clinical trial information is considered voluntary:

- Clinical trials of U.S. Food and Drug Administration (FDA)-regulated drug, biological, or device products that are **not** applicable clinical trials (ACTs) (referred to here as "non-ACT voluntary submissions")

- ACTs that were initiated on or before September 27, 2007, and that reached their primary completion date before December 26, 2007 (referred to here as "pre-FDAAA ACT voluntary submissions")

For both types, the regulations refer specifically to "clinical trials," thereby excluding the submission of information for observational studies from being considered voluntary submissions. In addition, because the Food and Drug Administration Amendments Act of 2007 (FDAAA) became law on September 27, 2007, only certain clinical trials for which clinical trial information was submitted on or after September 27, 2007, can be considered a voluntary submission.

Non-ACT Voluntary Submission

The first type of voluntary submission described in 42 CFR 11.60, a non-ACT voluntary submission, is a clinical trial of an FDA-regulated drug, biological, or device product that is not an ACT (see 42 CFR 11.60(a)(1)(i), 42 CFR 11.60(b)(1)(i), and 42 CFR 11.60(c)(1)(i)). The submission of a phase 1 trial of an FDA-regulated drug or biological product or a small clinical trial that evaluates the feasibility of an FDA-regulated device product is a non-ACT voluntary submission. The submission of a trial that studies only a behavioral (or other) intervention that is not an FDA-regulated drug, biological, or device product is not a voluntary submission (81 FR 65105). Therefore, submission of registration and/or results information for a clinical trial of an FDA-regulated product that would not otherwise meet the ACT definition as described in 42 CFR 11.10(a) or 11.22(b) would be considered a voluntary submission under 42 CFR 11.60. This means that non-ACT voluntary submissions would be identified based on the data elements specified in 42 CFR 11.28 (when provided) and outlined below:

- The Study Type is "Interventional"

- At least one of the following applies:

    - At least one Facility Location — Country is "United States" or a U.S. territory.

    - The response to U.S. Food and Drug Administration IND or IDE? is "Yes."

    - The response to Product Manufactured in and Exported from the U.S.? is "Yes."

- The response to Studies a U.S. FDA-regulated Drug Product? is "Yes," and/or the response to Studies a U.S. FDA-regulated Device Product? is "Yes."

- The Study Phase is "Early Phase 1" or "Phase 1" (for drug or biological products), or the Primary Purpose is "Device Feasibility" (for device products).

Pre-FDAAA ACT Voluntary Submission

The second type of voluntary submission described in 42 CFR 11.60, a pre-FDAAA ACT voluntary submission, is a clinical trial that meets all the ACT criteria found in 42 CFR 11.10(a) and 11.22(b) but for which submission of clinical trial registration information is not required because the trial was initiated on or before September 27, 2007, and reached its primary completion date before December 26, 2007 (see 42 CFR 11.60(a)(1)(ii), 42 CFR 11.60(b)(1)(ii), and 42 CFR 11.60(c)(1)(ii)). As noted previously, for such pre-FDAAA ACT voluntary submissions, information about the trial must have been submitted on or after September 27, 2007.

For additional information, see:

- National Institutes of Health (NIH): Voluntary Submission Flowchart and "Triggered Trials" Checklist (PDF) (June 2018)

- FAQ: How do I know if my clinical trial "Studies a U.S. FDA-regulated Drug Product" or "Studies a U.S. FDA-regulated Device Product" when evaluating whether it is an applicable clinical trial (ACT) subject to the regulation under the conditions specified in 42 CFR 11.22(b)? Specifically, for a trial conducted entirely outside the U.S.?

- NIH: Checklist and Elaboration for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT) (PDF) (June 2018)

What are the clinical trial information requirements for voluntary submissions under the regulation?

A responsible party must submit certain clinical trial information for trials subject to the voluntary submission requirements under 42 CFR 11.60. The information that must be submitted is determined by the initiation date (that is, the Study Start Date) and the Primary Completion Date and is described in 42 CFR 11.60(a)(1), 42 CFR 11.60(b)(1), and 42 CFR 11.60(c)(1)).

A responsible party who submits information for a trial subject to the voluntary submission requirements must also submit clinical trial information about certain other ACTs (referred to as "triggered trials") if clinical trial information for those ACTs has not already been submitted to ClinicalTrials.gov. These requirements are described in 42 CFR 11.60(a)(2)(ii), 42 CFR 11.60(b)(2)(ii), and 42 CFR 11.60(c)(2)(ii).

For additional information, see:

- NIH: Voluntary Submission Flowchart and "Triggered Trials" Checklist (PDF) (June 2018)

- FAQ: What types of clinical trials are considered voluntary submissions subject to the regulation?

What is a "triggered" trial under the regulation?
The voluntary submission of information for a clinical trial under 42 CFR 11.60 can trigger the requirement that information be submitted for other clinical trials (i.e., "triggered" trials) if certain conditions in the regulation are met. The triggering requirements in 42 CFR 11.60(a)(2)(ii) or 11.60(b)(2)(ii) apply if the voluntarily-submitted trial (either a "non-applicable clinical trial (non-ACT)" voluntary submission or a "pre-FDAAA applicable clinical trial (ACT)" voluntary submission) studies the use of a drug, biological, or device product for which the manufacturer (who is also the trial's responsible party) submitted an application or premarket notification to FDA on or after September 27, 2007, for approval, licensure, or clearance for the use studied in the clinical trial. Triggered trials for which clinical trial information must be submitted are those pre-FDAAA ACTs (that is, ACTs that were initiated on or before September 27, 2007, and that reached their primary completion date before December 26, 2007) that (1) study the same use of the drug, biological, or device product in the application or premarket notification to FDA and (2) are required to be submitted to FDA in an application or premarket notification for approval, licensure, or clearance to market the drug, biologic, or device product studied in the clinical trial. A study that does not meet the definition of an ACT under 42 CFR 11.10(a) (for example, a phase 1 clinical trial of a drug or biological product, a small feasibility study of a device product, or an observational study) would not be considered a triggered trial under 42 CFR 11.60.

For additional information, see:

- NIH: Voluntary Submission Flowchart and "Triggered Trials" Checklist (PDF) (June 2018)

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When must clinical trial information for a "triggered trial" be submitted to meet the requirements for voluntary submissions under 42 CFR 11.60?
The regulation requires a responsible party (who is also the manufacturer of the drug, biological, or device product studied in the voluntary submission) to submit clinical trial information for triggered trials no later than the later of the following two dates: (1) the date that the relevant application or premarket notification was submitted to FDA or (2) the date that clinical trial information was submitted to ClinicalTrials.gov for a trial subject to the voluntary submission requirements (42 CFR 11.60(a)(2)(iv)(B), 42 CFR 11.60(b)(2)(iv)(B), or 42 CFR 11.60(c)(2)(iv)(B)). The following scenarios relate to the timing of the submission of information for triggered trials:

- Scenario 1 — The responsible party voluntarily submits clinical trial information under 42 CFR 11.60 **after** the application or premarket notification is submitted to FDA. In this situation, if the application or premarket notification was submitted to FDA on or after September 27, 2007, the responsible party is required to submit the triggered trial information at the time the clinical trial information is voluntarily submitted under 42 CFR 11.60, regardless of how much time has passed between the application or premarket notification submission and the voluntary submission (42 CFR 11.60(a)(2)(iv)(B), 42 CFR 11.60(b)(2)(iv)(B), or 42 CFR 11.60(c)(2)(iv)(B)). For example, if the manufacturer submitted a new drug application (NDA) to FDA on January 1, 2008, and the responsible party voluntarily submitted registration and results information to ClinicalTrials.gov for one of the clinical trials required to be submitted to FDA for that NDA on January 1, 2018, the responsible party would also be required to submit the registration and results information for any other triggered clinical trials on the same date, that is, January 1, 2018 (42 CFR 11.60(a)(2)(iv)(B)).

- Scenario 2 — The responsible party voluntarily submits registration information under 42 CFR 11.60 **before** the application or premarket notification is submitted to FDA. In this situation, if the information was voluntarily submitted on or after September 27, 2007, the responsible party is required to submit registration information for the triggered trial by the time the application or premarket notification is submitted to FDA, regardless of how much time has passed since the voluntary submission (42 CFR 11.60(a)(2)(iv)(B), 42 CFR 11.60(b)(2)(iv)(B), or 42 CFR 11.60(c)(2)(iv)(B)). For example, if the responsible party voluntarily submitted registration information on January 18, 2018, for a clinical trial initiated on January 18, 2018, and the manufacturer is required by FDA to submit this clinical trial for an NDA that is submitted on January 1, 2020, the responsible party would also be required to submit the registration information for any other triggered clinical trials by the NDA submission date, that is, January 1, 2020 (42 CFR 11.60(c)(2)(iv)(B)).