Summary of Registration and Reporting Requirements for ClinicalTrials.gov

DHHS Final Rule for Clinical Trials Registration and Results Information Submission ("Final Rule") and the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information ("Policy")

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Background

ClinicalTrials.gov is an online registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. The purpose of ClinicalTrials.gov is to provide the public with readily accessible information about clinical trials on a wide range of diseases and conditions. ClinicalTrials.gov captures significant summary protocol information before and during the trial as well as summary results and adverse event information of a completed trial.

ClinicalTrials.gov was created as a result of the FDA Modernization Act of 1997 (FDAMA) which required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions.

Title VIII (Section 801) of the FDAAA of 2007 expanded registration requirements and established specific reporting requirements with legally defined timelines for the systematic reporting of trial results for certain trials. This led to the development of the clinical trial database, which was made available to the public September, 2008.

On September 16, 2016, the DHHS issued Final Rule (42 CFR Part 11) clarifying and expanding the registration and results information submission requirements of FDAAA 801. Simultaneously, the NIH issued a complementary final policy irrespective of whether the trials are covered by FDAAA requirements set in the DHHS Final Rule. This policy is complementary to the statutory and regulatory reporting requirements (Section 402(j) of the Public Health Service Act, as amended by Title VIII of the FDAAA of 2007 and 42 CFR Part 11).

Overview

The FDAAA established legal requirements for responsible parties to report specified clinical trial information for certain “applicable clinical trials” to ClinicalTrials.gov (https://www.clinicaltrials.gov). In addition to registration, the statute established a system and mandate for reporting summary results information within specific time frames, independent of possible journal publication. As described above, the HHS “Final Rule” was made available on September 16, 2016.

Registration and Reporting Rationale

- Provide potential participants with information about trials of interest
- Enable funders to determine need for new trials
- Provide more complete listing of trials to inform the medical evidence base
- Enable scientific community to examine overall state of research as a basis for engaging in QI efforts
- No structured, tabular, public database previously existed
- FDAAA requirements reflect “Minimum Reporting Data Set”
Basic information needed to understand trial results ('floor')

### Key Dates

- **Release Date:** September 16, 2016
- **Effective Date:** January 18, 2017
- **Compliance Date (with Final Rule):** April 18, 2017

➢ Applicable Clinical Trials (ACTs) initiated on/after effective date must follow registration requirements

◆ Applicable Clinical Trials (ACTs) that reach their **Primary Completion Date** (see definition below) on/after effective date must submit results information as specified in the Final Rule.

### Definitions (as interpreted in the “Final Rule”)

**“Applicable (Device) Clinical Trial (ACT)”**

1. A prospective clinical study of health outcomes comparing an intervention with a device product subject to Section 510(k), 515, or 520(m) of the Federal FD&C Act (21 U.S.C. 360(k), 21 U.S.C. 360e, 21 U.S.C. 360j(m)) against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes).

2. A pediatric postmarket surveillance of a device product as required under Section 522 of the FD&C Act (21 U.S.C. 3601)

3. OR

   3. A clinical trial of a combination product with a device primary mode of action under 21 CFR Part 3, provided that it meets all other criteria of the definition under this part [Source: 42 CFR 11.10(a); 81 CFR 65139].

**“Applicable (Drug) Clinical Trial (ACT)”** - A controlled clinical investigation, other than a Phase 1 clinical investigation, of a drug product subject to Section 505 (pg. 180) of the Federal FD&C Act (21 U.S.C. 355) or a biological product subject to Section 351 of the Public Health Service Act (PHS Act, 42 U.S.C. 262), where “clinical investigation” has the meaning given in 21 CFR 312.3 and “Phase 1” has the meaning given in 21 CFR 312.21. A clinical trial of a combination product with a drug primary mode of action under 21 CFR Part 3 is also an applicable drug clinical trial, provided that it meets all other criteria of the definition under this part [Source: 42 CFR 11.10(a); 81 CFR 65139].

**Expanded access use under Section 561 of the Federal FD&C Act is not an Applicable Clinical Trial.**

**Adverse Event** – Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to subject’s participation in the research.
Approved (or Cleared) Device – A device that is cleared for any use under Section 510(k) of the Federal FD&C Act, or approved for any use under Sections 515 or 520(m) of that Act.

Approved Drug – A drug that is approved for any use under Section 505 of the Federal FD&C Act, or a biological product licensed for any use under Section 351 of the Public Health Service Act.

Arm – A pre-specified group or subgroup of human subject(s) in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol.

Comparison Group – A grouping of human subjects in a clinical trial (other than an arm) that is or may be used in analyzing the results data collected during the clinical trial.

“Controlled” studies – Data collected on human subjects in the clinical trial will be compared to concurrently collected data or to non-concurrently collected data (e.g., historical controls, including a human subject’s own baseline data), as reflected in the pre-specified primary or secondary outcome measures. For purposes of this Rule, all clinical trials with one or more arms and pre-specified outcome measure(s) are controlled.

All interventional studies in humans with prespecified outcome measures, including those with one intervention group, are designed to evaluate a relationship between an intervention and an outcome, and would therefore be considered “controlled.” No implication as to the quality or relevance of the “control” is inferred for either single- or multigroup trials.

Ongoing – With respect to a clinical trial of a drug product (including a biological product) or a device product and to a date, that one or more human subjects is enrolled in the clinical trial, and the date is before the primary completion date of the clinical trial. With respect to a pediatric postmarket surveillance of a device product, ongoing means a date between the date on which FDA approves the plan for conducting the surveillance and the date on which the final report is submitted to the FDA.

Outcome Measure – A pre-specified measurement that will be used to determine the effect of an experimental variable on the human subject(s) in a clinical trial.

(Primary) Completion Date – 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. In the case of clinical trials with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. For a pediatric postmarket surveillance of a device product that is not a clinical trial, completion date means the date on which the final report of the pediatric postmarket surveillance of the device product is submitted to the FDA.

Essentially this is the date of final data collection for the prespecified primary outcome measure(s).

NOTE: under any circumstance NOT the date of analysis.

Primary Outcome Measure – The outcome measure(s) of greatest importance specified in the protocol, usually the one(s) used in the power calculation. Most clinical trials have one primary outcome measure, but a clinical trial may have more than one.
**Responsible Party** – The sponsor of the clinical trial (i.e., IND/IDE holder or the initiator of the study, considered the grantee organization for NIH-funded trials) as defined in 21 CFR 50.3; OR the principal investigator (PI) of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the PI 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 for submission of clinical information. For a pediatric postmarket surveillance of a device product that is not a clinical trial, the responsible party is the entity who the FDA orders to conduct the pediatric postmarket surveillance of the device product. There must be one (and only one) ‘responsible party’.

**Secondary Outcome Measure** – An outcome measure that is of lesser importance than a primary outcome measure, but is part of a pre-specified analysis plan (included in the SAP) for evaluating the effects of the intervention or interventions under investigation in a clinical trial and is not specified as an exploratory or other measure. A clinical trial may have more than one secondary outcome measure. Exploratory (or tertiary) measures for which there are no prespecified analytic plans are not considered secondary outcome measures. Reporting of these outcome measures is not mandatory but is encouraged.

**Serious Adverse Event** – An adverse event that results in any of the following outcomes:

- Death
- Life-threatening adverse event (as defined in 21 CFR 312.32)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the human subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of a substance use disorder.

**Study Completion Date** – 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.

<table>
<thead>
<tr>
<th>Criteria (Device)</th>
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<tbody>
<tr>
<td>□ The study is a pediatric postmarket surveillance of a device product as required by the FDA under Section 522 of the Federal FD&amp;C Act (21 U.S.C. 3601)</td>
</tr>
<tr>
<td>OR</td>
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<tr>
<td>□ Study type is interventional</td>
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Primary purpose is **NOT** device feasibility
Studies an FDA-regulated device product

**AND**

One or more of the following:
- At least 1 facility location is within the U.S. or its territories
- Product is manufactured in and exported from the U.S. (or one of its territories) for study in another country
- Conducted under an FDA IDE (has an FDA IDE number)

**Criteria (Drug)**

Study type is interventional
Study phase is **NOT** Phase 1
Studies an FDA-regulated drug product (including biologics)

**AND**

One or more of the following:
- At least 1 facility location for the clinical trial is within the U.S. or its territories
- Product is manufactured in and exported from the U.S. (or one of its territories) for study in another country
- Conducted under an FDA IND (has an FDA IND number)

**Submission Elements of the DHHS Final Rule**

**Registration:**

No Later Than 21 days after enrollment of first participant

- Exception to the registration timeline for a pediatric postmarket surveillance of a device product that is **not** a clinical trial
- Data elements:
  - Applicable Clinical Trial (ACT)
  - Pediatric postmarket surveillance of a device product that is **not** a clinical trial
  - Expanded access for an IND product studies in an applicable drug clinical trial
- After (Initial) Registration
  - Submitting updates
  - Making corrections

**Results:**

No Later Than 12 months after Primary Completion Date
• Exceptions to the timeline for results submissions:
  o Delayed submission of results information with certification if seeking approval, licensure, or clearance of a new use
  o Delayed submission of results with certification if seeking initial approval, licensure or clearance
  o Submitting partial results information
  o Extensions for “good cause”
  o Pediatric postmarket surveillance of a device product that is not a clinical trial

• Data elements:
  o Applicable Clinical Trial (ACT)
  o Pediatric postmarket surveillance of a device product that is not a clinical trial

### NIH Policy

**ALL NIH-funded** clinical trials, whether funded in whole or in part, regardless of study phase, type of intervention, or whether subject to regulation must be registered and summary results information reported to ClinicalTrials.gov.

- Applies to NIH-funded clinical trials where applications or proposals are received by NIH on or after January 18, 2017
- Applies to NIH-conducted clinical trials initiated on or after January 18, 2017
- Does not apply to a clinical trial that uses NIH-supported infrastructure which does not receive NIH funds to support its conduct

**Responsibilities as per Policy:**

1. Applicants seeking NIH funding will be required to submit a plan for the dissemination of NIH-funded clinical trial information that will address how expectations of this policy will be met
   a. If the NIH-funded clinical trial is an applicable clinical trial under the regulation and the awardee or investigator is the responsible party, the awardee or investigator will ensure that all regulatory requirements are met
   b. If the NIH-funded clinical trial is an applicable clinical trial under the regulation but the awardee or investigator is not the responsible party, the awardee or investigator will coordinate with the responsible party to ensure that all regulatory requirements are met
   ○ If the NIH-funded clinical trial is not an applicable clinical trial under the regulation, the awardee or investigator will be responsible for carrying out the tasks and meeting the timelines described in regulation (such tasks include registering the clinical trial in CT.gov and submitting results information to CT.gov)
2. Informed consent documents for clinical trials within all of the above categories are to include a specific statement relating to posting of clinical trial information at CT.gov
3. Each NIH-funded clinical trial should have only one entry in CT.gov that contains its registration and summary results information (expectations for clinical trial information and summary results will be included in the terms and conditions of the NIH award)

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**Exclusions**

The following types of studies are generally excluded from the registration and results submission requirements of FDAAA 801 (non-exhaustive list):

- Phase 1 drug trials, including studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes
- Small clinical trials to determine feasibility of a device or a clinical trial to test prototype devices, where the primary outcome measure(s) relates to feasibility and not to health outcomes
- Trials that do not include drugs, biologics, or devices (e.g., behavioral interventions)
- Non-interventional (observational) clinical research (e.g., cohort or case-control studies)
- Trials that were ongoing as of September 27, 2007 and reached the Primary Completion Date (see definition) before December 26, 2007

**NOTE:** Trials may be subject to the Voluntary Submission provision of FDAAA 801.

**FDAAA Decision Tree Tool for an Applicable Clinical Trial (flowchart)**


**Final Rule Cheat Sheet/FAQs**

**Q:** Who is subject to the Requirements?

**A:** Responsible party. The responsible party is the study sponsor (i.e., IND/IDE holder or the initiator of the study, considered the grantee organization for NIH-funded trials) OR a sponsor-designated PI who is responsible for conducting the study and has access to and control over the clinical data to analyze the data and publish results.

**Q:** Which clinical trials are subject to the Requirements ("Applicable Clinical Trials")?

**A:** Registration and results information reporting is required for any trial for which the following is true:

- The study is a pediatric postmarket surveillance of a device product as required by the FDA under Section 522 of the Federal FD&C Act (21 U.S.C. 3601)

**OR**

- Study type is interventional
- Primary purpose is NOT device feasibility
- Studies an FDA-regulated device product

**AND**

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☐ One or more of the following:
  o At least 1 US facility location
  o Product manufactured in and exported from the US
  o Conducted under an FDA IDE

OR (for Drug/Biologic)

☐ Study type is interventional
☐ Study phase is NOT Phase 1
☐ Studies an FDA-regulated drug product (including biologics)

AND

☐ One or more of the following:
  o At least 1 US facility location
  o Product manufactured in and exported from the US
  o Conducted under an FDA IND

It should be noted that ALL NIH-funded clinical trials, whether funded in whole or in part, regardless of study phase, type of intervention, or whether subject to regulation must be registered and summary results information reported to ClinicalTrials.gov.

Q: When does information need to be submitted to ClinicalTrials.gov?

For Registration:

**Submission:** In accordance with the FDA Amendments Act (FDAAA 801), registration is required within 21 days after enrollment of the first participant. The International Committee of Medical Journal Editors (ICMJE) and other journals require registration of clinical trials prior to enrollment of the first participant.

**Posting:** Generally, within 30 days after submission. For ACT of unapproved/uncleared devices, no earlier than FDA approval/clearance and no later than 30 days after FDA approval/clearance (i.e., delayed posting), unless a responsible party authorizes posting of submitted information prior to FDA approval/clearance.

For Reporting of Results:

**Submission - Standard deadline:** Within 12 months (1 year) after the date of final data collection for the prespecified primary outcome measures (= Primary Completion Date).

**Submission - Delayed w/certification:** May be delayed for up to 2 additional years (i.e., up to 3 years total after primary completion date) for trials certified to be undergoing commercial product development for initial FDA marketing approval/clearance or approval/clearance for a new use.

**Submission of partial results:** Deadlines are established for submitting results information for a secondary outcome measure or additional adverse information that has not been collected by the primary completion date.
Submission - Extension request: After receiving/reviewing requests, NIH may extend deadline for “good cause.”

Posting: Within 30 days after submission.

Q: What Registration and Reporting information is required?

For Registration of Applicable Clinical Trials initiated before 18 January 2017:

1. Descriptive information about the trial:
   - Brief Title
   - Brief Summary
   - Primary Purpose
   - Study Design
   - Study Phase (for an applicable drug clinical trial)
   - Study Type
   - Primary Disease or Condition Being Studied, or the Focus of the Study
   - Intervention Name
   - Intervention Type
   - Study Start Date
   - Expected Completion Date
   - Target Number of Subjects
   - Outcomes, Including Primary and Secondary Outcome Measures

2. Recruitment information:
   - Eligibility Criteria
   - Gender
   - Age Limits
   - Whether the trial accepts healthy volunteers
   - Overall Recruitment Status
   - Individual Site Status
   - Availability of Expanded Access for those who do not qualify for enrollment in the trial and how to obtain information about such access

3. Location/Contact information:
   - Name of the Sponsor
   - Responsible Party (by Official Title)
   - Facility Name and Contact Information (including City, State and Zip Code for each clinical trial location, or a toll-free number through which location information can be accessed)

4. Administrative Data:
   - Unique Protocol Identification Number
   - Other Protocol Identification Numbers, if any
   - U.S. FDA IND or IDE Protocol Number
   - Record Verification Date
For Registration of Applicable Clinical Trials initiated **on or after 18 January 2017**:

1. **Descriptive information about the trial:**
   - Brief Title
   - Official Title
   - Brief Summary
   - Primary Purpose
   - Study Design
   - Study Phase (for an applicable drug clinical trial)
   - Study Type
   - Pediatric Postmarket Surveillance of a Device Product, for an applicable device clinical trial that is a Pediatric Postmarket Surveillance of a Device Product
   - Primary Disease or Condition Being Studied in the Trial, or the Focus of the Study
   - Intervention Name(s), for each intervention studied
   - Other Intervention Name(s), for each intervention studied
   - Intervention Description, for each intervention studied
   - Intervention Type, for each intervention studied
   - Studies an FDA-regulated Device Product/Drug Product
   - Device Product Not Approved/Cleared by the FDA, if any studied intervention is a device product
   - Post prior to FDA Approval/Clearance, for an applicable device clinical trial that studies at least one device product not previously approved/cleared by the FDA
   - Product Manufactured in and Exported from the U.S., if the entry for FDA IND or IDE Number indicates that there is no IND/IDE for the clinical trial, and the entry(ies) for Facility Information include no facility locations in the U.S. or its territories
   - Study Start Date
   - Primary Completion Date
   - Study Completion date
   - Enrollment
   - Primary Outcome Measure Information, for each primary outcome measure
   - Secondary Outcome Measure Information, for each secondary outcome measure

2. **Recruitment information:**
   - Eligibility criteria
   - Sex/Gender
   - Age Limits
   - If the trial accepts healthy volunteers
   - Overall Recruitment Status
   - If ended prematurely, Why Study Stopped
   - Individual Site Status
   - Availability of Expanded Access. If available for an IND, an expanded access record must be submitted in accordance with 42 CFR 11.28(c), unless previously submitted
3. **Location/Contact information:**
   - ☐ Name of the Sponsor
   - ☐ Responsible Party (by Official Title)
   - ☐ Facility Information

4. **Administrative Data:**
   - ☐ Unique Protocol Identification Number
   - ☐ Secondary ID
   - ☐ U.S. FDA IND or IDE Number
   - ☐ Human Subjects Protection Review Board Status
   - ☐ Record Verification Date
   - ☐ Responsible Party Contact Information

1 *Subsets of the above elements are required for Pediatric Postmarket Surveillance of a Device Product that is not a clinical trial and for Expanded Access Records.*

For Reporting Results of Applicable Clinical Trials where the Primary Completion Date is **before 18 January 2017** (if collected):

Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with 42 CRF 11.54, if the Applicable Clinical Trial 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 sections 402(j)(3)(C) and 402(j)(3)(I) of the PHS Act. (42 CFR 11.42(a)(1)), as follows:

1. **Demographic and baseline characteristics of patient sample**
   - ☐ A table of the demographic and baseline data collected overall and for each arm of the clinical trial to describe the patients who participated in the clinical trial, including the number of patients who dropped out of the clinical trial and the number of patients excluded from the analysis, if any.

2. **Primary and secondary outcomes**
   - ☐ The primary and secondary outcome measures and a table of values for each of the primary and secondary outcome measures for each arm of the clinical trial, including the results of scientifically appropriate tests of the statistical significance of such outcome measures.

3. **Point of contact**
   - ☐ A point of contact for scientific information about the clinical trial results.

4. **Certain agreements**
   - ☐ Whether there exists an agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of participants) between the sponsor or its agent and the principal investigator (unless the sponsor is an employer of the principal investigator) that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.
5. **Serious adverse events**

☐ A table of anticipated and unanticipated serious adverse events grouped by organ system, with number and frequency of such event in each arm of the clinical trial.

6. **Frequent adverse events**

☐ A table of anticipated and unanticipated adverse events that are not included in the table described above that exceed a frequency of 5 percent within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial.

☐ If the Applicable Clinical Trial 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 *not* required to submit results information.

For **Reporting Results of Applicable Clinical Trials where the Primary Completion Date is on or after 18 January 2017** (if collected):

Unless a waiver of the requirement to submit clinical trial results information is granted in accordance with 42 CRF 11.54, if the Applicable Clinical Trial studies a drug, biological, or device product, then the responsible party is required to submit the results information specified in section 42 CFR 11.48, as follows:

1. **Participant Flow:**

☐ Information documenting the progress of human subjects through a clinical trial, by arm, including the number who started and completed the trial. This includes the following elements:

   - Participant Flow Arm Information
   - Pre-assignment Information
   - Participant Data

2. **Demographic and Baseline Characteristics:**

☐ Information documenting demographic and baseline measures and data collected by arm or comparison group and for the entire population of human subjects who participated in the clinical trial. This includes the following elements:

   - Baseline Characteristics Arm/Group Information
   - Baseline Analysis Population Information
     - Overall Number of Baseline Participants
     - Overall Number of Units Analyzed
     - Analysis Population Description
   - Baseline Measure Information
     - Name and Description of the Measure
     - Measure Type and Measure of Dispersion
     - Unit of Measure
   - Baseline Measure Data
3. Outcomes and Statistical Analyses:
   - Information for each primary and secondary outcome measure by arm or comparison group, including result(s) of scientifically appropriate statistical analyses that were performed on the outcome measure data, if any. This includes the following elements:
     - Outcome Measure Arm/Group Information
     - Analysis Population Information
       - Number of Participants Analyzed
       - Number of Units Analyzed
       - Analysis Population Description
     - Outcome Measure Information
       - Name of the Specific Outcome Measure
       - Description of the Metric Used to Characterize the Specific Outcome Measure
       - Time point(s) at which the Measurement was Assessed for the Specific Metric
       - Outcome Measure Type
       - Measure Type and Measure of Dispersion or Precision
       - Unit of Measure
   - Outcome Measure Data
   - Statistical Analyses

4. Adverse Event Information:
   - Information to describe the methods for collecting Adverse Events during an Applicable Clinical Trial:
     - Time Frame – The specific period of time over which AE information was collected and for which information is submitted
     - AE reporting description (if the AE information collected in the clinical trial is collected based on a different definition of AE and/or SAE from that used in Final Rule)
     - Collection approach used to collect AE information, whether systematic or non-systematic
   - Information for completing three tables summarizing anticipated and unanticipated AEs collected during an Applicable Clinical Trial:
     - Table of all SAEs grouped by organ system, with the number and frequency of each event by arm or comparison group
     - Table of all AEs, other than SAEs, that exceed a frequency of 5% within any arm of the clinical trial, grouped by organ system, with the number and frequency of each event by arm or comparison group
Table of all-cause mortality, with the number and frequency of deaths due to any cause by arm or comparison group (= all cause deaths)

Information for each table specified above must include the following elements, unless otherwise specified:

- Adverse Event Arm/Group Information
- Total Number Affected. The overall number of human subjects affected, by arm or comparison group, by:
  - SAEs
  - AEs other than SAEs that exceed a 5% frequency within any arm of the clinical trial
  - Deaths due to any cause
- Total Number at Risk. The overall number of human subjects included in the assessment, by arm or comparison group, for:
  - SAEs
  - AEs other than SAEs that exceed a 5% frequency within any arm of the clinical trial
  - Deaths due to any cause
- Adverse Event Information. For the two tables described directly above, a description of each type of SAE and other AE that is not an SAE and exceeds a frequency of 5% within any arm of the clinical trial, consisting of the following attributes:
  - Descriptive term for the AE
  - Organ system associated with the AE
- Adverse Event Data. For the two tables described above, and for each AE listed IAW the Adverse Event Information above:
  - Number of human subjects affected by such AE
  - Number of human subjects at risk for such AE

5. Protocol and Statistical Analysis Plan (SAP):

- A copy of the approved protocol and the SAP (if not included in the protocol), including all amendments that have been approved by a human subjects protection review board before the time of submission and that apply to all clinical trial Facility Locations
  - To be submitted at time of results information reporting (option to submit earlier)
  - ICFs are optional

6. Administrative Information:

- Results Point of Contact for scientific information about clinical trial results information:
  - Name or official title of the Point of Contact
  - Name of the affiliated organization
  - Telephone number and email address of the Point of Contact

7. Additional Clinical Trial Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products

1 Subsets of the above elements are required for Pediatric Postmarket Surveillance of a Device Product that is not a clinical trial.
Q: What are the Requirements for updating clinical trial registration information once a Human Subjects Review Board approves a protocol amendment?

For applicable clinical trials initiated on or after 18 January 2017, or for which registration information was voluntarily submitted pursuant to 42 CFR 11.60(c), if 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 no later than 30 calendar days after the protocol amendment is approved by a human subjects protection review board. 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.

Q: What other Registration updates are required to be made to Applicable Clinical Trials in ClinicalTrials.gov?

- Responsible Parties should update their records in ClinicalTrials.gov **within 30 days** of a change to any of the following:
  - “Recruitment Status” and “Overall Recruitment Status”
  - “Primary Completion Date” and “Completion Date”

Other changes or updates to the record, such as protocol amendments, must be made at least every 12 months. It is recommended that the “Record Verification Date” be updated at least every 6 months for studies that are not yet completed, even if there were no changes to the record.

Q: Must Applicable Clinical Trials with no external sources of funding (“unfunded” studies) be registered in ClinicalTrials.gov?

Applicable clinical trials with no external sources of funding are **not** excluded from the requirements described in FDAAA 801. In general, an unfunded study should be registered by the Sponsor. When an investigator is considered the Sponsor (e.g., a Sponsor-Investigator), the study should be registered by 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.

Q: How should results information be submitted for Applicable Clinical Trials that are terminated prior to completion, or otherwise stopped prematurely, and for which no data were collected for one or more Outcome Measures?

If no participants were ever enrolled, the Overall Recruitment Status in ClinicalTrials.gov should be set to “Withdrawn.” No results information will need to be submitted.

For trials that were terminated after participants were enrolled, any available data should be provided. If no data are available for any of the Outcome Measures, zero (“0”) should be specified for the “Number of
Participants Analyzed in each Arm/Group” and the data fields should be left blank. An explanation should be provided in the “Analysis Population Description” to indicate why no participants were analyzed and, if appropriate, information should be provided in the “Limitations and Caveats” module. Even if data are not entered for Outcome Measures, available data for the enrolled participants should be included in the “Participant Flow, Baseline Characteristics, and Adverse Events” modules.

**Factoids**

- HHS Final Rule - 16 SEP 2016
- NIH Complementary Final Policy - Submit registration and results information for all NIH-funded clinical trials, whether or not the trials are covered by the Food and Drug Administration Amendments Act (FDAAA) requirements.
- Regulation requires the submission of results information for ACTs regardless of the approval status of studied products (under the statute, submission of basic results information was required only for ACTs of products previously approved for at least one use)
- The NIH is prohibited from posting registration information submitted for any ACTs of a device product that has not been previously approved/cleared by the FDA. However, parties responsible for such trials may authorize the NIH to post registration information prior to FDA approval/clearance. This will enable interested responsible parties to conform to ICMJE (and related) policies which require posting at trial initiation.
- Narrative summaries are not required
- QC review of submitted trial information is conducted by the NIH. Review is designed to detect errors/deficiencies and inconsistencies in submissions. Previously, the NIH did not post submitted information that did not meet QC criteria. Current rule requires NIH to post all submitted information on CT.gov within 30 days after receipt even if there are outstanding QC issues. Records for ACTs that do not meet QC criteria are still returned w/comments. Responsible parties will have 15 days to correct registration errors and 25 days to correct results information records. Records that still do not meet QC criteria after 30 days will be posted with a disclaimer and, possibly, a general explanation of concerns about quality. An NCT number will not be assigned until QC criteria are met. Once criteria are met, disclaimers will be removed.
- Under the statute, responsible parties, including, for example, grantee institutions, could be held accountable for noncompliance, with the potential for substantial civil monetary penalties, the withholding of grant funding from HHS agencies, and criminal proceedings.

**Timelines**

The CT.gov data-entry system, (PRS), is ready to support all regulatory submissions. Parties have until 18 April 2017 (90 days after effective date) to reach conformance with final rule.

In general, ACTs initiated on/after the effective date (18 January 2017) must follow requirements for registration. ACTs that reach their primary completion date on or after this effective date must submit results information as specified in the Final Rule.
Investigator and Coordinator FAQs

1. Should you register your research project with ClinicalTrials.gov
   YES, Register your study at the NIH website, ClinicalTrials.gov.

   YES, if you want to publish the results of your study
   If you wish to publish your study in a peer-reviewed journal, then it is highly likely that the journal
   will expect your study to have been registered with ClinicalTrials.gov. Thousands of journals have
   adopted the policy of the International Committee of Medical Journal Editors (ICMJE) that requires
   registration in a publicly available register.

   YES, because in some cases, IT'S THE LAW
   A small subset of studies is required by law to be registered with ClinicalTrials.gov. The FDA
   Amendments Act (FDAAA) of 2007 required that most prospective studies involving regulated drugs,
   biological products, and medical devices must be registered on ClinicalTrials.gov. The law also
   requires reporting of “basic results” and adverse events for a subset of these studies. In addition,
   ALL NIH-funded clinical trials, whether funded in whole or in part by the NIH, regardless of study
   phase, type of intervention, or whether subject to regulation, must be registered and summary
   results information reported to ClinicalTrials.gov.

2. When do I have to register my study?
   ICMJE requires that you register prior to enrollment of your first study participant. The law (i.e.,
   Final Rule (42 CFR Part 11) requires that a study be registered within 21 days of enrollment of the
   first participant. In accordance with the Final Rule (42 CFR Part 11), you must also update your
   CT.gov records at least every 12 months, or within 30 days of a change in recruitment status.

3. When do I have to post basic results?
   The law requires that a subset of basic information be posted on ClinicalTrials.gov for any study in
   which the study product is approved for any use. For example, if you are studying an approved drug
   for a new use, you must register basic results. You must post this information within 12 months of
   the “Primary Completion Date” – defined by CT.gov as the final data collection point for the primary
   endpoint. Please note that you may not wait until complete data analysis of your project is completed
   to post basic results, if such completion falls outside the required time frame.

4. What are the consequences if I don’t register?
   The consequences for non-compliance can include fines from the FDA or NIH, or the withholding of
   grant funds for you individually or for the entire institution. Other consequences include rejection for
   publication in top journals (even for studies not required by law to register).

5. What Are The Penalties for failing to register?
   According to the FDA/NIH (Food and Drug Amendments Act of 2007): Penalties may include civil
   monetary penalties up to $10,000 fine for failing to submit or for submitting fraudulent information
to ClinicalTrials.gov. After notification of noncompliance, the fine may go up to $10,000 per day until resolved. For federally funded grants, penalties may include the withholding or recovery of grant funds.

According to the ICMJE: Unregistered trials will not be considered for publication in journals that adhere to ICMJE standards. This penalty has not changed over time.