ClinicalTrials.gov Results and Adverse Events

A Companion Guide for the Responsible Party

The Food and Drug Administration Amendments Act (FDAAA) requires results and adverse events for applicable clinical trials (ACT) to be made available to the public through a free, publicly accessible database. The NIH requires all NIH funded clinical trials to make results and adverse events publicly available. The overall benefit from this requirement aims to increase public trust and transparency in clinical research.

The NIH and the FDA require summary results and adverse event data be made available no later than 12 months after the study primary completion date. This date is specified by the Responsible Party and is listed in the ClinicalTrials.gov registration. The primary completion date is defined by the final rule 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.” (42 CFR 11.10)

The HHS final rule and NIH Complimentary policy went into effect on January 18, 2017. Enforcement by the FDA and NIH began April 19, 2017. The final rule and policy apply, respectively, to applicable clinical trials and NIH-funded clinical trials initiated on or after January 18, 2017.

This guide is a resource for KUMC faculty and staff. The guide covers uploading study results and adverse event data into ClinicalTrials.gov.

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Background Information

What is an “Applicable Clinical Trial (ACT)”?
An APPLICABLE CLINICAL TRIAL is the term used in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) to designate the scope of trials that may be subject to the registration and reporting requirements in FDAAA.

Generally speaking, if the study meets the following criteria, it is an ACT:
1. Involves a drug or device subject to FDA regulation
2. Not a phase I or small feasibility (for devices) study
3. Involves at least one site in the US

For a ClinicalTrials.gov checklist to help you identify an ACT according to FDAAA requirements, see: https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

For an NIH flowchart to help you identify an ACT according to FDAAA requirements, see: https://grants.nih.gov/clinicaltrials_fdaaa/docs/Flow_chart-ACT_only.pdf

Who is the “Responsible Party”?
The “Responsible Party” refers to the entity or individual who is responsible for registering a trial in a clinical trial registry data bank (i.e. ClinicalTrials.gov). They are the ONLY user who is able to “release” the initial record and future updates to it for public view. There is ONE responsible party per study. This is to prevent a study from being registered multiple times.

The Responsible Party is considered to be:
1. The Sponsor: A person who initiates a clinical investigation, but who does not actually conduct the investigation OR a corporation or agency that uses one or more of its own employees to conduct a clinical investigation it has initiated, OR;
2. The principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, 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 this subsection for the submission of clinical trial information

More Information on ACT and Responsible Party
For the complete statutory definition of an ACT and an elaboration on the FDA’s current thinking, see http://prsinfo.ClinicalTrials.gov/ElaborationsOnDefinitions.pdf

NIH Funded Studies
The NIH requires results reporting for all NIH-supported clinical trials, regardless of whether or not they are subject to FDAAA (http://grants.nih.gov/clinicaltrials_fdaaa/at-a-glance.htm).
Results and Adverse Event Registration

Overview of the Results Section
When you open a study registration, you are taken to the “Record Summary” page. This page has four main sections:

1. Record Status
2. Protocol Section
3. Document Section
4. Results Section

The first step to creating results for submission is to click “Enter Results” link in the Results Section. Results are due within 12 months of the primary completion date. Completing the results section can be a time consuming process. Make sure to give yourself enough time to have the results approved and publicly posted by the site within 12 months of study completion. It generally takes ClinicalTrials.gov QA about 30 days to review the initial results submission.

It is recommended the study team member most familiar with the data and/or the study statistician enter or assist in entering results data.

Results for at least the primary outcome measure are required within 12 months of the primary completion date. Result data may not be available for all outcome measures at this time point. If data are not yet available for all outcomes, only data available for primary outcome measure(s) for each arm of the study must be entered. Data for secondary measures are due within 12 months of the study completion date, or the final data collection date for the study. If the primary and study completion dates are different, you may need to enter data into clinicaltrials.gov on multiple occasions.

There are seven modules in the results section. Data in each module are reviewed and approved by ClinicalTrials.gov before the results are considered final. Required elements of each module are open to change.

The modules are:

1. Participant Flow
2. Baseline Characteristics
3. Outcome Measures
4. Adverse Events
5. Certain Agreements
6. Limitations and Caveats
7. Results Point of Contact

Participant Flow
Purpose is to document participants that started, dropped out/withdraw/pulled out of, and completed the study (identical in purpose to a consort flow diagram, but represented as tables). Each enrolled participant needs to be captured in this section. Data reported in this section will be cross checked against future sections of the results. Make sure to accurately report any person that did not complete the study.
Data Reported in Section:
1. Number Started: Number of participants at the beginning of the period. How many patients were consented?
   a. The number reported here MUST match the final actual enrollment total in the protocol section.
2. Number Completed: Number of participants at the end of the period. How many consented subjects completed all study-related activities?
3. Not Completed: If any subject did NOT complete the entire study, they must be reported (Started ≠ Completed). The total number of participants accounted for by all reasons must equal the number of participants listed under "Not Completed."
   a. For each person that did not complete the study, a reason must be provided. Options include:
      i. Adverse Event, Death, Lack of Efficacy, Lost to Follow-Up, Physician Decision, Pregnancy, Protocol Violation, Withdrawal by Subject, Other (if other selected, provide reason)

Arms:
You will be asked to confirm information about each arm of the study. The system will copy over information from the protocol section. Now is the time to make sure information about the arms is accurate! Update each arm/group as needed. You will re-use the same info for other parts of the results section. Information for each arm should include:
1. Arm/Group Title: Label used to identify the arm or comparison group. Using only numbers is insufficient, i.e. Arm 1, Arm 2. Be more descriptive, i.e. Study Drug Name, Dosage
2. Arm/Group Description: Brief description of the arm or comparison group to distinguish it from other arms/groups in the trial. It is useful to include intervention information, i.e. dosage, form, frequency.

Example of Participant Flow Table:

<table>
<thead>
<tr>
<th>Recruitment Details:</th>
<th>[not required] Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and types of location (e.g., medical clinic), to provide context.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-assignment Details:</td>
<td>[not required] Description of any significant events and approaches for the overall study (e.g., wash out, run-in, transition) following participant enrollment, but prior to group assignment. For example, an explanation of why enrolled participants were excluded from the trial before assignment to groups.</td>
</tr>
</tbody>
</table>
Common Errors in the Participant Flow Section:
- The Arm/Group Description does not include additional details about the interventions administered (e.g., dosage, dosage form, frequency of administration).
- The Enrollment number in the protocol section (i.e., 7) conflicts with the number of participants started in the Participant Flow module (i.e., 10).

Baseline Characteristics
This section captures demographic and other data on enrolled subjects. Age and Gender data are required to be entered. Other commonly used options include Race, Ethnicity and Region of Enrollment (best practice). Include other characteristics relevant to the study.

If the study enrolls subjects, but is stopped early, you will still be asked to complete this section.

Overall Number of Baseline Participants: should match the number “started” from Participant flow section. If it does not, you need to provide an explanation.

Two different data types can be utilized in the section:
1. Continuous: measure of central tendency and measure of dispersion (mean, standard deviation)
2. Categorical: a count or measure of central tendency and measure of dispersion
Data must be provided for each arm and ALSO for total started. This is the only section where statistical data are required to be reported for total enrolled. For example, if you are reporting the continuous age in a two arm study that enrolled 50 subjects, data required:

1. Arm 1: Intervention + SOC – mean/standard deviation data for 25 subjects
2. Arm 2: Placebo + SOC – mean/standard deviation data for 25 subjects
3. Total: All subjects – mean/standard deviation data for 50 subjects

**Example of Final Participant Flow Table:**

<table>
<thead>
<tr>
<th>Arm/Group Title</th>
<th>Drug A and Standard of Care (SOC)</th>
<th>Placebo and Standard of Care (SOC)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm/Group Description</td>
<td>Participants received 100mg pills of Drug A to be taken by mouth daily for 3 months. This was in addition to SOC.</td>
<td>Participants received 100mg matching placebo pills to be taken by mouth daily for 3 months. This was in additional to SOC.</td>
<td></td>
</tr>
<tr>
<td>Overall Number of Baseline Participants</td>
<td>25</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Baseline Analysis Population Description</td>
<td><em>If participant population differs for a baseline measure, the number of participants should be included in here. Explanation of how the number of participants for analysis was determined.</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Continuous; Mean (Standard Deviation), Units: years</td>
<td>30.00 (5.50)</td>
<td>35.75 (7.75)</td>
<td>34.55 (6.75)</td>
</tr>
<tr>
<td>Gender, Male/Female; Measure Type: Number, Units: participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>Body Mass Index (BMI); Mean (Standard Deviation), Units: kg/m^2</td>
<td>21.50 (5.00)</td>
<td>25.50 (6.00)</td>
<td>23.00 (5.00)</td>
</tr>
</tbody>
</table>

**Outcome Measures**

Study results must be entered according to the ClinicalTrials.gov format and structure. You are required to enter a table of values for each of the listed outcome measures. All outcome measures in the protocol must be included in the ClinicalTrials.gov registration! This may require additional data analysis. Provide ample time to complete this section.

Remember, ClinicalTrials.gov is meant to be utilized by the public. Try to present data and information so the average person understands what the numbers represent. This is no small task but will make the study registration and ClinicalTrials.gov a more effective tool.
Example of Outcome Measure Table:

<table>
<thead>
<tr>
<th>Measure Type</th>
<th>Primary, Secondary, Other</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome Measure Title*</th>
<th>Name of the measure used to assess the effect of experimental variables in the trial. Should be worded so people unfamiliar with the study can understand it</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome Measure Description</td>
<td>Additional information describing outcome measure.</td>
</tr>
<tr>
<td>Outcome Measure Timeframe*</td>
<td>Time point when outcome measure is assessed. Each outcome measure can only have one time point. If multiple outcomes are based on the same underlying measure assessed at different time points (i.e. 8 weeks, 12 weeks and Final Visit), then each unique combination of measurement and time frame is entered as a separate outcome measure (i.e. Change from Baseline to Week 8 in MMSE, Change from Baseline to Week 12 in MMSE, etc.).</td>
</tr>
<tr>
<td>Safety Issue?</td>
<td>(Yes/No)</td>
</tr>
<tr>
<td>Arm/Groups</td>
<td>Drug A and Standard of Care (SOC)</td>
</tr>
<tr>
<td>Number of Participants Analyzed*</td>
<td>For the outcome reported. If not the same as number completed the study, provide explanatory comment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure Type</th>
<th>Dispersion Type</th>
<th>Measure Type</th>
<th>Dispersion Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous/Categorical Data</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
</tr>
</tbody>
</table>

| Unit of Measure | How is data being reported? e.g., participants, lab values, mm Hg, units on a scale |

Common Errors in the Results Section:

- Number of Participants Analyzed is not consistent with other parts of the results.
  - If the number of participants analyzed is not consistent with numbers provided in any of the rows in the Participant Flow Module, verify numbers and explain the discrepancy in Analysis Population Description, as appropriate.

- When an outcome measure uses a scale, not enough information about the scale is provided.
  - Information required by the site is:
    - All scale ranges (i.e., minimum and maximum scores) required to interpret any values in the data table. For example, if the *total* score is reported, the *total* range should be provided. If subscale scores are reported, the range for each subscale should be provided.
    - For each scale range provided, specify which values are considered to be a better or worse outcome (i.e., Do higher values represent a better or worse outcome?).
    - If subscales are combined to compute a total score, consider indicating how subscales are combined (summed, averaged, etc.).

- The unit of measure is not appropriate for the outcome measure.
Double check the unit of measure is accurate for the reported outcome. Some common units of measure are:

- Percent change between two periods = percent change
- When a scale is used = units on a scale

The time frame is not in preferred site format.

- Preferred format example: Change from Baseline to Month 6 OR, if time frame is based on snapshot of time in the future, acceptable to only include that time, i.e. Month 12.
- Inconsistency between unit and measure and reported data, i.e. hours of sleep per night, reported data of 48 hours.

**Adverse Events**

Data for this module is reported using two tables:

1. Serious Adverse Events
2. Other Adverse Events

The site requires all serious and other adverse events to be reported that exceed a frequency threshold of 5%. It is optional to report events that occurred less frequently than a 5% threshold.

When entering adverse events, ensure the following:

1. The number of participants affected is entered for every event.
   a. When one or more subjects experience an event in one arm, but none do in another arm, you still need to enter “0” affected for the latter.
   b. Be sure to keep track if one subject experienced an event multiple times. You can have a greater number of events than number of participants affected, but you cannot have a greater number of participants affected than at risk.
2. The number of participants at risk is consistent with information provided in the participant flow module.
   a. The number at risk for each adverse event entered will be equal to the number that started in each arm. Do not enter the “total” number enrolled for the entire study.
3. The same adverse event cannot be in both the serious and other tables.
   a. It may be acceptable for the same adverse event term to be in both tables, however, use the term or additional description fields to differentiate between the two events.

**Limitations and Caveats**

This optional section may be used to describe any significant limitations of the study. Limitations may include not reaching the target number of participants needed to achieve target power and statistically reliable results or technical problems with measurements leading to unreliable or uninterpretable data.

**Certain Agreements**

Certain agreements include results information restrictions on principal investigators after the completion of a study.

This section asks the following questions:

1. Are all principal investigators employees of the sponsor?
2. Is there an agreement between the sponsor (or its agent) and any non-employee PI(s) that restricts the PI’s rights to discuss or publish trial results after the Primary Completion Date?

3. Are there agreements with multiple non-employee PIs and is there a disclosure restriction on at least one PI?

Results Point of Contact
Enter information for the point of contact for scientific information about the clinical study results information. Required fields are:
- Name or Official Title: The person, listed either as a person’s name or a position title, who is designated the point of contact.
- Organization Name: Full name of the designated individual’s organizational affiliation
- Phone: Office phone number of designated official, using format 123-456-7890.
- Email: Electronic mail address of the designated individual.

Document Section – NEW REQUIREMENT

Applicable clinical trials and NIH-funded clinical trials initiated on or after January 18, 2017 require upload of the full study protocol and statistical analysis plan as part of results information submission. Informed consent forms are optional and may be uploaded at any time.

Uploaded documents must meet the following requirements:

- Each document must include a cover page with the Official Title of the study, NCT number (if available), and date of the document.

- Uploaded study documents should be the most recent version reviewed by a human subjects protection review board (if applicable).

- Documents must be uploaded in Portable Document Format Archival (PDF/A) format. It is strongly encouraged that the PDF/A file also be consistent with the PDF Universal Accessibility (PDF/UA) format, to optimize accessibility.

- For each uploaded document, provide information on Document Type (Study Protocol, Statistical Analysis Plan, Informed Consent Form, or Study Protocol with SAP and/or ICF) and the date on which the uploaded document was most recently updated.
References


PRS Results Data Element Definitions: https://register.clinicaltrials.gov/prs/html/results_definitions.html

PRS Training Materials: https://clinicaltrials.gov/ct2/manage-recs/present

PRS FAQs: https://clinicaltrials.gov/ct2/manage-recs/faq


ClinicalTrials.gov Templates & Checklists: https://prsinfo.clinicaltrials.gov/results_table_layout/ResultSimpleForms.html


NIH Grantee Roles and Responsibilities: https://grants.nih.gov/clinicaltrials_fdaaa/faq.htm#B

Title 42 Part 11: https://www.ecfr.gov/cgi-bin/text-idx?SID=e617ee4da22678f934787ed565bbaa5a&mc=true&node=pt42.1.11&rgn=div5