CLINICALTRIALS.GOV

STUDY REGISTRATION & REPORTING OF RESULTS

Contents:

I. REGULATORY BACKGROUND

ClinicalTrials.gov is a registry of federally and privately supported clinical research maintained by the National Library of Medicine (NLM) and the National Institutes of Health (NIH). The registry provides easy access to information about a wide range of studies and it is aimed at increasing transparency and improving public awareness of research. Information about individual clinical trials is added to ClinicalTrials.gov by registering the trial and reporting its results. It is essential to understand which studies must be registered and who is responsible for ensuring that registration (and reporting of results, if required) takes place. The following provides detailed information to help you determine if your research should be registered with ClinicalTrials.gov, and if so, offers guidance to complete the registration and submission of trial results according to the applicable requirements and best practices modeled after institutions from the Association of American Universities (AAU).

A. Why is Registration of Trials and Reporting of Results Required?

1. Federal regulations and journal publication standards require that investigators register certain clinical studies in a publicly accessible database. ClinicalTrials.gov was created to support compliance with such regulations and standards.

   a. The FDA Amendments Act of 2007 ("FDAAA") imposes that "Applicable Clinical Trials" must be registered in ClinicalTrials.gov and a sub-set of those trials also have results reported. ***Applicable clinical trials generally include prospective trials involving drugs, biological products, and devices subjects to FDA regulation***.

   b. The NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information[1] ("NIH Policy") is complementary to the reporting requirements of FDAAA and establishes the expectation that all investigators conducting clinical trials funded in whole or in part by NIH will ensure that these trials are registered and results information is submitted to ClinicalTrials.gov. NIH defines a clinical trial as a ***research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.***

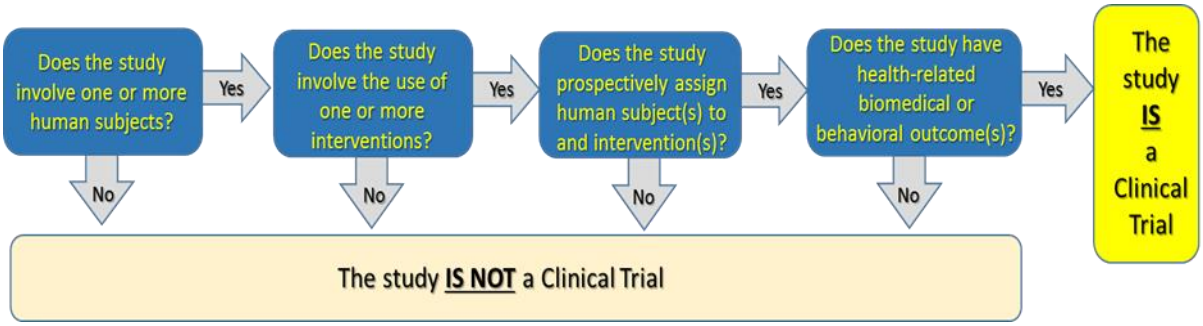

Fig. 1. NIH Definition of Clinical Trial Decision Tree. NIH offers case studies illustrating the application of this decision tree.

   c. The International Committee of Medical Journal Editors ("ICMJE") policy (adopted by over 1,000 journals) is broader in scope than FDAAA in requiring which types of trials must be registered. ***The ICMJE policy applies to research that prospectively assigns human subjects to intervention or comparison groups in order to look at the cause-and-effect relationship between an intervention and a heath outcome.***

2. ClinicalTrials.gov contains information on publicly and privately funded clinical studies on a wide range of diseases and conditions. The registry aims to support improved transparency and to reduce duplication of effort by enabling easy access to information about clinical trials to patients, their family members, health care professionals, researchers and the public.

[1] For detailed information, see Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information, NIH Clinical Research Policy, and NIH Policy p. 22.

3. **Noncompliance** has serious repercussions for individuals, research teams, and institutions including but not limited to:

FDAAA	NIH Policy	ICMJE
▪ Public notices of noncompliance and violations ▪ Withholding of grant funds ▪ FDA sanctions ▪ Civil monetary penalties (**up to $10,000/day**)	▪ Withholding of funds ▪ Termination of grant(s)	▪ Cannot publish in journals following ICMJE policy and other select journals

B. Which Trials Require Registration and Submission of Results to ClinicalTrials.gov?

1. **FDAAA:**

a. **Registration and Results Submission Requirements:** FDAAA 801 requires trial registration and results submission for "**Applicable Clinical Trials**", which include:[2]

i. Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
ii. Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies; and
iii. Interventional studies (with one or more arms[3]) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

- The trial has one or more sites in the United States;
- The trial is conducted under an FDA investigational new drug ("IND") application or investigational device exemption ("IDE"); and/or
- The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research.

b. **Registration Exclusions:** Pursuant to FDAAA, the following is a nonexclusive listing of types of trials that are generally excluded from required registration and submission of results; however, registration of such studies and study results may be voluntarily submitted to ClinicalTrials.gov. These exclusions no not apply to NIH funded studies (as described below in section 2. "NIH Policy"):

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[2] For more detailed information, see "Which Trials Require Registration and Submission of Results to ClinicalTrials.gov?" at FDAAA 801 Requirements, Elaboration of Definitions of Responsible Party and Applicable Clinical Trial, , and Guidance [from NIH Office of Extramural Research] on New Law (Public Law 110-85) Enacted to Expand the Scope of ClinicalTrials.gov Registration.

[3] "Arm" means a pre-specified group or subgroup of participant(s) in a clinical trial assigned to receive specific intervention(s) (or no intervention) according to a protocol

i. Phase I drug trials, including studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes;

ii. Small clinical trials to determine the feasibility of a device or a clinical trial to test prototype devices, where the primary outcome measure relates to feasibility and not to health outcomes;

iii. Trials that do not include drugs, biologics, or devices (such as behavioral interventions);

iv. Non-interventional clinical research. ClinicalTrials.gov defines Observational Studies[4] as follows: "In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health (such as cohort or case-control studies);

- Clinicaltrials.gov encourages registration and results reporting of observational studies. Additionally, some journals, sponsors, and international organizations, such as the European Medicines Agency (EMA) require registration and results reporting of observational trials.

v. For Applicable Clinical Trials that include a device not previously approved or cleared by FDA for any use and that need to be registered, full posting of the trial information on ClinicalTrials.gov can be delayed until after the device has been approved or cleared.[5]

vi. Even if your trial fits one of the exclusions from registration requirements listed above:

- Consult the "instructions to authors" for journals in which you hope to publish to ensure that you will not be prohibited from publication in a journal because of the journal's registration requirements.

- Review the contractual agreement with the trial sponsor to ensure that the sponsor does not require registration and results submission.

c. **NIH Requirements for Applicants for Grant Funding:** NIH grantees must certify compliance with FDAAA 801 in their competing applications and noncompeting continuation progress reports for any NIH grant that supports a clinical trial, even if the grantee is not the Responsible Party for registering trials and submitting trial results to ClinicalTrials.gov.[6]

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[4] For more detailed information about observational studies, see Registration of Observational Studies.

[5] For more detailed information, see Delayed Posting Data Element and "Which Trials Must Be Registered and Have Results Submitted to ClinicalTrials.gov?" at FDAAA 801 Requirements.

[6] For more detailed information about compliance with FDAAA by NIH grantees, see What NIH Grantees Need to Know About FDAAA.

2. **NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information ("NIH Policy"):**

   a. **Registration Requirements and Results Submission Requirements**:

      i. All clinical trials, regardless of study phase or type of intervention, that are funded by grant applications, contracts, or other transactions submitted to NIH on or after January 18, 2017, must register and report results with ClinicalTrials.gov.

      ii. The NIH Policy's definition of clinical trial is broader than the FDAAA's definition of an Applicable Clinical Trial and includes:

         - Phase I clinical trials of an FDA regulated product
         - Trials of interventions not regulated by the FDA, including surgical and/or behavioral interventions
         - Small feasibility studies of devices, or pilot trials designed to examine the feasibility of an approach.

      iii. Awardees undertaking clinical trials covered by the NIH Policy must ensure that the submission and updating of the same type of registration and results information, and in the same timeframes, as Responsible Parties whose trials are subject to the Final Rule.[7]

   b. **Registration and Results Submission Exclusions**: Under the NIH Policy, the following trials are not subject to mandatory registration and submission of results:[8]

      i. A clinical trial sponsored by NIH and awarded before January 18, 2017, where the clinical trial does not meet the FDAAA's definition of Applicable Clinical Trial.

      ii. A clinical trial that uses NIH-supported infrastructure but does not receive NIH funds to support conducting the clinical trial, where the trial does not meet the FDAAA's definition of Applicable Clinical Trial.

      iii. However, NIH encourages researchers to register and submit results with ClinicalTrials.gov for all types of trials.

   c. **Requirements for Applicants for NIH Grant Funding**: Effective January 18, 2017, applications for NIH funding for any clinical trial are subject to the NIH Policy and must include as part of the application a plan for registering trials and submitting results to ClinicalTrials.gov. The NIH Policy applies to all clinical trials funded in whole or part by NIH

   d. **The administrative costs of complying with the NIH Policy** are normally covered by indirect costs. However, with the prior approval of NIH, grantees are permitted to charge the salaries

[7] On September 16, 2016, the Public Health Service issued a "Final Rule," 45 CFR Part 11, expanding the requirements for submitting registration and results information for "Applicable Clinical Trials". The Final Rule has an effective date of January 18, 2017. Responsible Parties will have 90 calendar days (until April 19, 2017) after the effective date to come into compliance with the requirements of the Final Rule. A Summary of the Final Rule is available at https://www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information.

[8] Source: NIH Policy pp. 16 and 22

of administrative and clerical staff as a direct cost to the award, as such staff could assist investigators in meeting their responsibilities under the NIH Policy.

3. **ICMJE:**

   a. **Registration Requirements**: The policy of the International Council of Medical Journal Editors (ICJME) requires the registration of all prospective clinical studies in a World Health Organization-approved primary registry such as ClinicalTrials.gov.[9] Some journals have additional specifications for which studies must be registered. Please consult the instructions to authors for the journals in which you hope to publish the results of your trial to avoid a prohibition from being able to publish in a particular journal due to the journal's registration requirements.

   b. ICJME policy does not require, but encourages, reporting of clinical trial results.

C. Who Is Responsible for Registering Trials and Submitting Results?

1. FDAAA requires the "**Responsible Party**" [10] to register and submit results of an Applicable Clinical Trial.

   a. The sponsor of the clinical trial, or

   b. The principal investigator (PI) of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, if: 1) the PI is responsible for conducting the trial, 2) the PI has access to, and control over, the data from the clinical trial, 3) the PI has the right to publish the results of the trial, and 4) the PI has the ability to meet all of FDAAA's requirements for the submission of clinical trial information.

2. If a trial is being conducted under an IND or IDE, then the IND/IDE holder is the Responsible Party, regardless of how the trial is funded.[11]

   a. If the IND/IDE is issued in the name of the PI, the PI is the Responsible Party.

      If the IND/IDE is issued in the name of the sponsor of the research, the sponsor of the research is the Responsible Party.

3. For trials not conducted under an investigational new drug (IND) application or an investigational device exemption (IDE):

   a. Contractual agreements with industry/pharmaceutical sponsors of trials typically designate the industry/pharmaceutical sponsor as the Responsible Party.

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[9] For more detailed information, see the ICJME Editorial, "Is This Clinical Trial Fully Registered? — A Statement from the International Committee of Medical Journal Editors."

[10] For more detailed information regarding "Responsible Party" and "Sponsor," see Elaboration of Definitions of Responsible Party and Applicable Clinical Trial and Responsible Party data element.

[11] For more detailed information, see ClinicalTrials.gov: Requirements and Implementation Strategies and Identifying the "Responsible Party" under FDAAA for Applicable Clinical Trials Conducted Under NIH Grants.

b. Government (federal and state) funded grants designate the grant recipient, University of Delaware as the Responsible Party. However, **UD delegates this responsibility to the PI,** making the PI the Responsible Party.

c. Where no external funding exists for the trial, the PI is the Responsible Party by default.

4. Exceptions exist. Check the agreement/contract with the sponsor (or the grant's terms and conditions) regarding who is responsible for trial registration and results submission.

5. If it is unclear who is responsible for registering an applicable clinical trial, investigators should consult with the sponsor, funding agency, and/or other study investigators to define who the responsible party will be.

D. When Must I Register A Trial?

1. **By FDAAA** and **NIH Policy:** The Responsible Party (that is, the sponsor or designated PI) must register the trial **no later than 21 days after enrollment of the first subject.**[12]

2. **ICJME Compliance**: The ICJME requires registration **before the first subject is enrolled**.[13]

   a. The ICMJE will accept registration in any of the World Health Organization-approved primary registries, including ClinicalTrials.gov. However, registering the trial with ClinicalTrials.gov fulfills both the regulatory and the ICMJE criteria for registration.

   b. The ICMJE does not define the timing of "before the first subject is enrolled", but best practice is considered that registration should be completed before a subject is consented for a trial.

3. **Required Registration Updates:**

   a. Responsible Parties should update their records within 30 days of a change to any of the following:

      i. Recruitment Status (accrual activity at a study site)

      ii. Overall Recruitment Status

      iii. Completion Date

   b. Other changes or updates to the record 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.

   c. See How to Edit Your Study Record for details on updating study information.

4. **Is IRB Approval Required before registering a study with clinicaltrials.gov?**

   a. In accordance with guidance from the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA), the clinical trial listing does not require IRB approval if the "Overall Recruitment Status" of the study is "Not yet recruiting."

[12] Source: FDAAA 801 Requirements; NIH Policy p. 21
[13] Source: ICMJE – Clinical Trial Registration

b. IRB approval is required before recruitment of study subjects begins, as subject recruitment is considered to be part of the informed consent and subject selection process.

c. The **University of Delaware requires IRB approval prior to the registration of a study in clinicaltrials.gov**

E. When Must I Report Results?

1. **FDAAA and NIH Policy**: Clinical trial results, including adverse events, must be reported within **12 months** after the trial's Completion Date, which is defined 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"***. Reporting of Results must occur even when a protocol is terminated earlier than initially planned.[14]

2. **ICJME Compliance:** The ICMJE encourages posting of clinical trial results in clinical trial registries *but does not require it*. The ICMJE does not consider as "prior publication" the posting of trial results in ClinicalTrials.gov if results are limited to a brief (500 words or less) structured abstract or tables that include subjects enrolled, key outcomes, and adverse events.

3. **When is Delayed Submission of Results Permitted?**

   a. **Delayed Submission of Results:** The Responsible Party may delay the submission of results beyond the 12-month required timeline by submitting a certification to clinicaltrials.gov that an Applicable Clinical Trial meets either of the following conditions:

      i. The trial is of a drug or device that has not been approved for marketing by the FDA for any indication, in which case result reporting will be required within 30 days of initial approval by the FDA;

      ii. The trial is of a drug or device for which the manufacturer has filed or is preparing to file an application seeking approval of the new use studied in the trial, in which case result reporting will be required within 30 days of initial approval by the FDA; or

      iii. A request for a delay that "demonstrates good cause" has been granted by the NIH Director.

      iv. Submit certifications for delayed results within ClinicalTrials.gov. After logging into the study in ClinicalTrials.gov, proceed to the "Delay Results" link in the "Results Section" of the Record Summary for the study in ClinicalTrials.gov.[15]

F. Additional Requirements: Informed Consent

[14] Source: FDAAA 801 Requirements; NIH Policy p. 21

[15] For more detailed information of delayed results submission, see slides 19-23 of Overview of FDAAA and Other Trial Registration Policies.

1. Pursuant to FDA Guidance[16], and NIH Policy[17] the following exact statement must be included in the informed consent documents of studies to be registered in ClinicalTrials.gov:

   "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time"

II. PROCEDURES

A. How Do I Obtain an Account with ClinicalTrials.gov?

1. University of Delaware (UD) has an organizational account with ClinicalTrials.gov. Registration is completed through the menu-driven Protocol Registration System ("PRS") by entering the organization name (enter "UDelaware") and your clinicaltrials.gov username and password.
   a. **University of Delaware has a PRS Administrator account managed by the Director of Research Compliance at UD, do not create PRS "individual account" when registering with ClinicalTrials.gov.**[18]
2. **Obtaining a username and password:** If you do not have an account with ClinicalTrials.gov (i.e., no username and password), proceed to https://clinicaltrials.gov/:
   a. Click "Submit Studies", and then click "How to apply for an account".
   b. Towards the bottom of the page, click the link, "PRS Administrator Contact Request Form." Complete the contact request form for the appropriate Organization (University of Delaware).
   c. You will receive an email from clinicaltrials.gov with the email address for the University of Delaware Protocol Registration System (PRS) Administrator account, clinicaltrials@udel.edu. Email the UD PRS Administrator account and request a username and password.
      i. **You must complete** the PRS Administrator Contact Request Form in clinicaltrials.gov in order to establish an account.
   d. If you do not know if you have an account or have forgotten your username, use the same steps as above to verify your username.

B. How Do I Register a Trial?

1. Once a username and password has been obtained, proceed to the ClinicalTrials.gov "PRS Login Page", enter the **Organization (UDelaware)**, **Username, and Password**.

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[16] For detailed information, see FDA Regulatory Guidance at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf.
[17] Source: NIH Policy p. 23
[18] For more detailed information, see Obtaining a PRS Account.

2. Complete all fields[19] as to information related to the trial. Once all of the information for the trial has been entered in the PRS record and marked as complete, an automated email will be sent to the UD PRS Administrator account. Upon completion of the administrative review, a UD PRS Administrator will approve and release the record to ClinicalTrials.gov, where the PRS team will review the record for quality control purposes prior to posting on the ClinicalTrials.gov website.
3. For basic help with using PRS, review the "Quick Start Guide" and the "PRS User's Guide" found in the "Help" section of the PRS top main menu, which is accessible after logging in ClinicalTrials.gov with your username and password.

C. How do I Submit Trial Results?

1. Enter Organization (UDelaware), your username, and your password on the "PRS Login Page" (https://clinicaltrials.gov/ct2/manage-recs/register)
2. Update the "Protocol Section" and release (submit) the record:
   a. Ensure that the information in the Protocol Section is up-to-date before starting the Results Section; e.g., the Overall Recruitment Status, Study Start Date, Primary and Study Completion Dates, Actual Enrollment, and arm and intervention information.
   b. Begin results submission after the updated record has been published on ClinicalTrials.gov.
3. Enter the required and optional results data elements. Scientific information is submitted as four separate modules: **Participant Flow**, **Baseline Characteristics**, **Outcome Measures and Statistical Analyses**, **and Adverse Events**. The process of submitting results information to ClinicalTrials.gov is conceptually similar to preparing a manuscript for publication in a journal. An individual familiar with the study design and data analysis (such as the clinical investigator or study statistician) will need to be involved in order to accurately summarize the results information in the tabular format required and to ensure that the results are consistent with the ClinicalTrials.gov review criteria. The modules allow for the entry and display of information in a series of data tables with supporting notes but without narrative conclusions about the results. The scientific information instructions section provides detailed information on how to prepare the submission of each module and it includes links to instructional online presentations:
   a. Participant Flow: a tabular summary of the progress of participants through each stage of a study, by study arm or comparison group. It includes the numbers of participants who started, completed, and dropped out of each period of the study based on the sequence in which interventions were assigned. The module accommodates a wide range of study designs and allows for the description of key events following study enrollment but prior to group assignment.
   b. Baseline Characteristics: a tabular summary of the data collected at the beginning of the study for all participants, by study arm or comparison group. These data include demographics, such as age and gender, and study-specific measures (e.g., systolic blood pressure prior to exercise treatment)

[19] For definitions of the data elements used during registration see https://prsinfo.clinicaltrials.gov/definitions.html

c. Outcome Measures and Statistical Analyses: a tabular summary of outcome measure values, by study arm or comparison group. It includes tables for each prespecified Primary Outcome and Secondary Outcome and may also include other prespecified outcomes, post hoc outcomes, and appropriate statistical analyses.

d. Adverse Events: a tabular summary of all anticipated and unanticipated *serious adverse events* and a tabular summary of anticipated and unanticipated *other adverse events* exceeding a specific frequency threshold.

i. Serious Adverse Any untoward or unfavorable medical occurrence in a participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

ii. Serious adverse events and any adverse event that exceeds a frequency threshold of 5% within any arm of the clinical trial must be reported. Threshold to report 'other' adverse events may be set differently by different sponsors.

4. For a description of criteria that should be addressed before releasing (submitting) the record, see "ClinicalTrials.gov Results Review Criteria".

5. Preview, inspect, and release (submit) the record.

6. When the record is released, an automated email will be sent to the UD PRS Administrator. Upon completion of the administrative review, the UD PRS Administrator will approve and release the record to ClinicalTrials.gov, where a ClinicalTrials.gov staff member will review the record for quality control purposes prior to posting the results on the ClinicalTrials.gov website.

7. Resources for the submission of results:

a. "Basic Results Data Element Definitions", contains descriptions of each required data item.

b. Results data preparation checklists, simple results templates for each module, required data, and a view of data elements in a tabular form are listed in the "Scientific Information" section of the "How to "Submit Your Results" guidance on ClinicalTrials.gov.

c. "Helpful Hints" contains tips on entering results data, including three examples of common study models (parallel design, crossover design, and diagnostic accuracy studies) and measure types.

D. Additional Resources:

1. There is a link at the bottom of each page on clinicaltrials.gov to submit a ticket for help: "CONTACT NLM HELP DESK".

2. ClinicalTrials.gov may be contacted with questions or for guidance via email at register@clinicaltrials.gov.

a. 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).

b. Be detailed in your request.

c. ClinicalTrials.gov generally responds to all emails within 1 business day.