EMORY | WOODRUFF HEALTH SCIENCES CENTER | Emory Clinical Research Office

Clinical Trial Determinations & ClinicalTrials.gov for Investigator-Initiated Studies

- Overview & Requirements -

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What is a Clinical Trial (CT)?

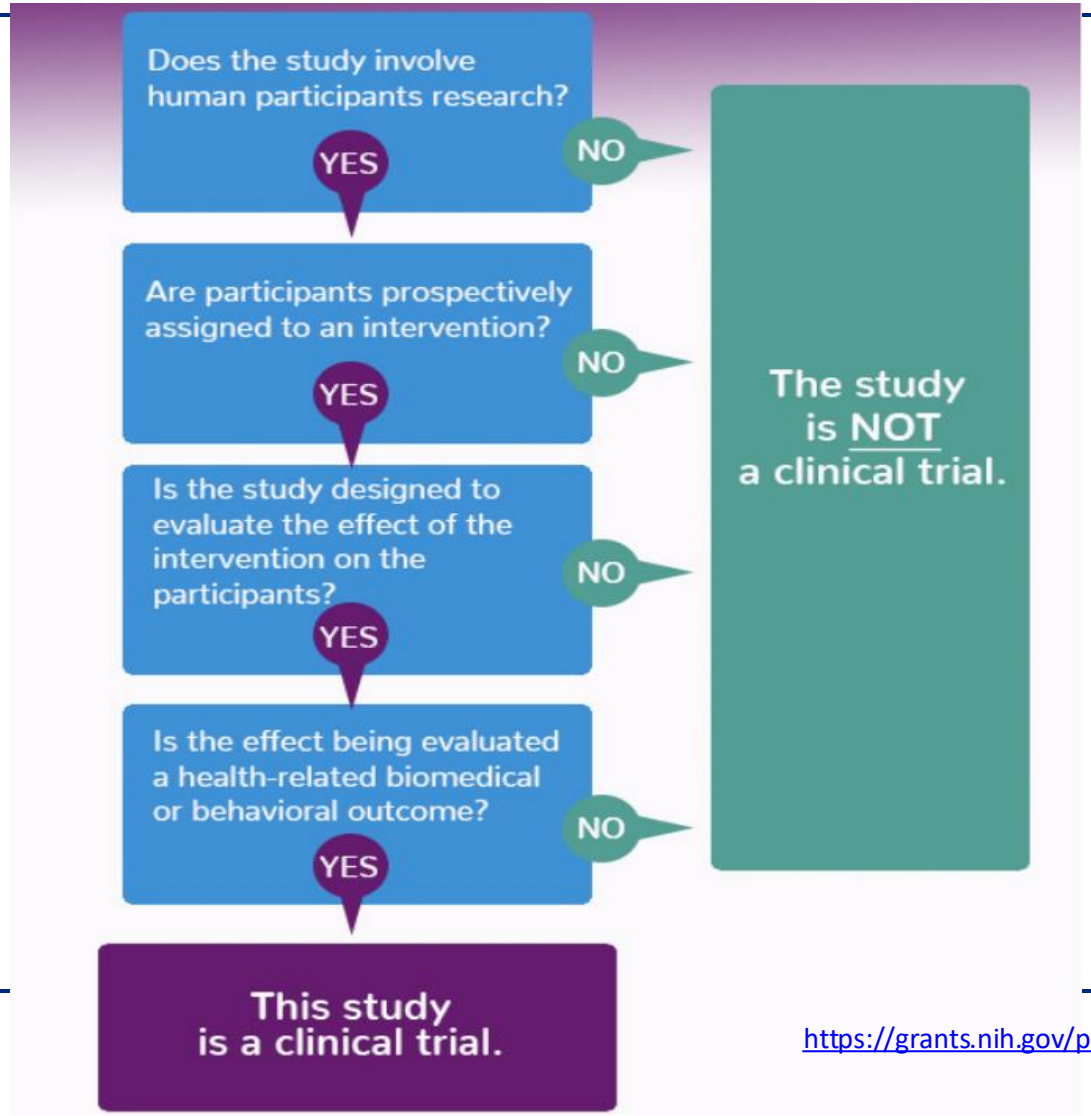
- Investigational drugs and devices (FDA-regulated) studies*
  - Safety
  - Efficacy

  **Note: these are the studies that meet the FDA "applicable clinical trial" definition*

- Some behavioral/social science studies (e.g., lifestyle changes, educational programs)

- Some mechanistic exploratory studies (research designed to understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention.)

NIH Decision Tree for Clinical Trial Definition



Note: Consult NIH Case Studies to assist with determinations

****Revised October 23, 2014**

https://grants.nih.gov/policy/clinical-trials/CT-decision-tree.pdf

NIH Clinical Trial Definition

NIH Disclaimer: These questions contain terminology—human participants, prospective assignment, intervention, health-related biomedical or behavioral outcome—that may mislead you if you aren't mindful of how NIH defines them.

- ***Human Subjects***
  - This aspect is fairly straightforward. However, the designation does not apply to secondary studies using existing unidentifiable biological specimens, data collected without identifiers, or data that are publicly available.

https://www.niaid.nih.gov/grants-contracts/determine-whether-nih-considers-your-mechanistic-study-clinical-trial

NIH Clinical Trial Definition

- ***Prospective Assignment***
  - NIH refers here to a predefined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a CT.

  - Randomization is not a requirement for a study to be a CT as long as the assignment of the research subjects is predefined. Note: a single-arm trial qualifies as a predefined assignment.

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NIH Clinical Trial Definition

- ***Intervention***
  - NIH defines intervention as "a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints."
  - If the study is designed to evaluate the effect of the intervention on the participants, then the study is a CT.
    - If the study generates data that are not used to measure an effect on the participants but only to assign the participants to a group or category (e.g., disease severity), then the study is likely not a CT.
  - Thus, **purpose is paramount**. Evaluate whether the prospectively-assigned intervention is intended to make and evaluate a change in a biomedical/biobehavioral outcome. Otherwise, the manipulation is not an intervention.
    - Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and diagnostic strategies.

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NIH Clinical Trial Definition

- ***Health-Related Biomedical or Behavioral Outcome***
  - This refers to the pre-specified goals or conditions that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.
  - That definition is broad and goes beyond efficacy of an intervention; for example, it includes safety outcomes.

- Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and positive or negative changes to quality of life.

https://www.niaid.nih.gov/grants-contracts/determine-whether-nih-considers-your-mechanistic-study-clinical-trial

Points of Note with NIH Clinical Trial Determinations

A study is considered to meet the NIH definition of a clinical trial <u>even if</u>:

- The study uses healthy participants, or does not include a comparison group (e.g., placebo or control)
- The study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- The study utilizes a behavioral intervention

A study is NOT considered to meet the NIH definition of a clinical trial if:

- The study is intended solely to refine measures.
- The study involves secondary research with biological specimens or health information.
- Surveys
- Questionnaires
- User preferences, focus groups
- Secondary research with biospecimens or health information
- Educational studies with outcomes focusing on memorization or retention & recall of information to assess teaching methods

NIH Clinical Trial Determinations for NIH-funded studies

- For NIH-funded research, **Emory University defers to the grant and/or NIH Program Officer's (PO) determination** as to whether or not a study is considered a clinical trial. Emory never makes this determination for NIH-funded studies.
  - This information should be confirmed by the investigator with the NIH PO, preferably in writing, if there is a question.
    - *Information regarding whether the study is considered a clinical trial per the NIH can be further validated in the Eforms application/eRA Commons e-application and is listed on the grant. The funding mechanism can also be indicative.*

Animals: N
Humans: Y
Clinical Trial: Y
Current HS Code: 20
HESC: N
HFT: N
Special Topics:
Data Management Sharing

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Deconstructing voice therapy: Towards enhanced communication outcomes	Yes

https://www.niaid.nih.gov/grants-contracts/determine-whether-nih-considers-your-mechanistic-study-clinical-trial

FDA Definition of an “Applicable Clinical Trial” (ACT)

- “Applicable clinical trials” include the following:

  - Trials of drugs and biologics: Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to Food and Drug Administration (FDA) regulation
  - Trials of devices (see note): 1) Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and 2) pediatric postmarket surveillance required by FDA

  Applicable Clinical Trials generally include interventional studies (with one or more arms) 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 application or investigational device exemption
  - The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research

FDA Checklist for "Applicable Clinical Trials" (ACTs)

Question	Yes	No
1. Is the study interventional (a clinical trial)? *Study Type* data element is "Interventional"	☐	☐
2. Do ANY of the following apply (is the answer "Yes" to at least one of the following sub-questions: 2a, 2b, OR 2c)?	☐	☐
a. Is at least one study facility located in the United States or a U.S. territory? *Facility Location – Country* data element is "United States," "American Samoa," "Guam," "Northern Mariana Islands," "Puerto Rico," "U.S. Virgin Islands," or other U.S. territory.		
b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)? *U.S. Food and Drug Administration IND or IDE Number* data element is "Yes."		
c. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country? *Product Manufactured in and Exported from the U.S.* data element is "Yes."		
3. Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)? *Studies a U.S. FDA-regulated Device Product* data element is "Yes" and/or *Studies a U.S. FDA-regulated Drug Product* data element is "Yes."	☐	☐
4. Is the study other than a Phase 1 trial of a drug and/or biological product or is the study other than a device feasibility study? For drug product trials, *Study Phase* data element is NOT "Phase 1" and for device product trials, *Primary Purpose* is NOT "Device Feasibility."	☐	☐

Interventional is defined in the final rule to mean, with respect to a clinical study or a clinical investigation, that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes. [42 CFR 11.10(a); 81 FR 65140-41]

Clinical Trial is defined in the final rule as a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes. [42 CFR 11.10(a); 81 FR 65139]

https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT that is required to be registered under 42 CFR 11.22.

Applicable Clinical Trials (ACTs) - Exclusions

- Some clinical trials may be excluded from the FDA definition, even if other definitions apply. For example:

Exclusions

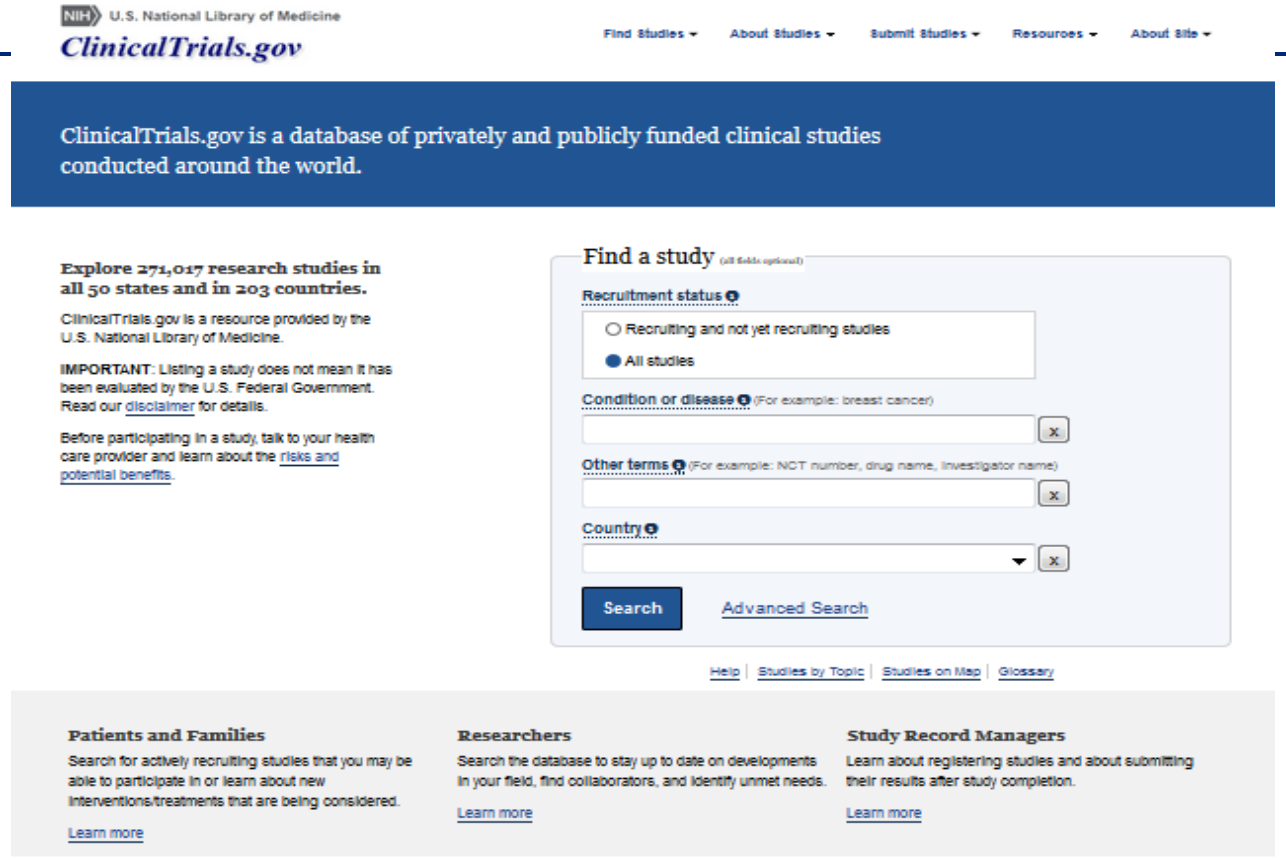
The following types of studies are generally excluded from the registration and results submission requirements of FDAAA 801 (see note). This is not a complete list.

- Phase 1 drug trials, including studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes (see note)
- 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 (see note)
- Trials that do not include drugs, biologics, or devices (such as behavioral interventions)
- Noninterventional (observational) clinical research (such as cohort or case-control studies)
- Trials that were ongoing as of September 27, 2007, and reached the Completion Date (see Primary Completion Date data element on ClinicalTrials.gov) before December 26, 2007 (see note)

Additional ClinicalTrials.gov Requirements/Applications

- **CT Definition under International Committee of Medical Journal Editors (ICMJE):** For publication in ICMJE-governed journals
  - "Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."
    - Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes)
    - Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events
- **CMS (billing) Requirements:** It is "mandatory to report a clinical trial number on claims for items/services provided in clinical trials that are qualified for coverage as specified in the Medicare National Coverage Determination (NCD) Manual, Publication 100-03, section 310.1." *(Note: CT determination is not relevant to requirement)*

ClinicalTrials.gov – Brief Overview



- ClinicalTrials.gov is a national registry of research studies conducted in the U.S. and around the world
- A new Final Rule by the FDA and a new NIH policy became effective in 2017 that affects ClinicalTrials.gov and the Requirements for Registration & Reporting for clinical trials

Scope & Applicability of ClinicalTrials.gov Requirements

FDA Final Rule	NIH Policy	International Committee of Medical Journal Editors (ICMJE)
- "Applicable clinical trials" of FDA-regulated drug, biologics, or devices - Does not apply to Phase 1 trials - Dose not apply to small feasibility device studies	- All clinical trials funded (wholly or partially) by NIH - Applies to clinical trials meeting NIH definition of a CT (includes non-drug/non-device trials, as well as behavioral/social research) - Includes Phase 1 trials - NIH applicants required to submit plan outlining how they will comply with clinical trial information dissemination	- Studies intended for publication and meeting the ICMJE definition for a clinical trial

Penalties for Failure to Register, Update, or Report Results

FDA Final Rule	NIH Policy	ICMJE
- Judicial remedies for violations include injunctions and criminal penalties by the FDA and DOJ - Civil monetary penalties up to $14,274 per day - For federally-funded CTs, grant funding withheld if reporting cannot be verified - Identification of CT record as non-compliant in ClinicalTrials.gov	- Suspension or termination of grant or contract funding to PI or Institution - Considered in future funding decisions - Identification of CT record as non-compliant in ClinicalTrials.gov	- Inability to publish in ICMJE-governed journals (http://www.icmje.org/journals-following-the-icmje-recommendations/)

Points to Remember with CT Determinations

- It is important to note that the use of words like “observational” and the avoidance of the phrase “clinical trial” in a protocol have no bearing on whether or not a study is deemed a clinical trial. The decision has to be made independently based on the use of the NIH decision tree, the ACT checklist, and the protocol specifications.
- IND and IDE exempt studies are still considered applicable clinical trials, as they are still FDA-regulated.
- The term “clinical trial” is often misused, but does (as demonstrated) have an expanding scope in research.
- If a study is a drug or device applicable clinical trial (ACT), it automatically meets the NIH definition of a clinical trial (*Emory’s standard definition of a CT*).
- Research billing, “routine care”, and/or the qualifying or non-qualifying status of a research study has no bearing on whether or not a study is deemed a clinical trial.
  - Of note, many clinical trials are designed around routine care to encourage participation by patients in clinical research.

Points to Remember with ClinicalTrials.gov Requirements

- Investigator-initiated studies should be registered (receive NCT#) prior to enrollment of the 1st participant to meet all requirements.
- Some study fields should be updated within 15 or 30 calendar days on ClinicalTrials.gov:
  - Protocol changes—including recruitment status, completion dates, and approved amendments—must be updated promptly.
- Results reporting is due within one year of the study completion dates by federal law and/or NIH Policy, as applicable.
  - Reminder to assess enrollment feasibility after 6 months without enrollment, as a full year of no enrollment may result in overdue results reporting once the completion date has been more than a year.

Points of Consideration for IRB Submitted Protocols

1 Clinical Trial = 1 Protocol (IRB Submission) = 1 NCT #

Why does this matter?

- This often occurs with NIH-funded studies wherein a grant can contain multiple studies, etc.

Other Reminders:

- There can only be one patient population per protocol (inclusion/exclusion) for CT.gov purposes and primary and secondary outcome measures define the reporting requirements per federal policy/law.
- At the end of the study during reporting of results, the final IRB protocol gets uploaded to ClinicalTrials.gov and is reviewed by the NIH in conjunction with summary results for the overall study.
- Study protocols should have well-defined primary and secondary outcome measures. For studies required to be registered on ClinicalTrials.gov (NIH-funded CTs and/or ACTs), the results for both of these outcome measures is required per NIH Policy and federal regulations, as applicable to the study.

IRB NIH & FDA Requirement Reminders

- **Dissemination of Information for NIH-funded Studies & ACTs**

  - **Informed Consent Documents:**
    - Both NIH-funded CTs & FDA ACTs must **include a specific statement relating to posting of clinical trial information at 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.*

For Additional Information:

- Information regarding NIH clinical trial determinations can be found at the following locations:
  - https://grants.nih.gov/policy/clinical-trials/CT-decision-tree.pdf
  - https://grants.nih.gov/policy/clinical-trials.htm

- More information regarding determining ACTs is available at:
  - https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

- More information regarding the Final Rule & the NIH Policy for ClinicalTrials.gov are available at:
  - https://clinicaltrials.gov/policy/fdaaa-801-final-rule
  - https://clinicaltrials.gov/policy/reporting-requirements

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Questions?

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