



What is Clinicaltrials.gov, and do you need to register your study?

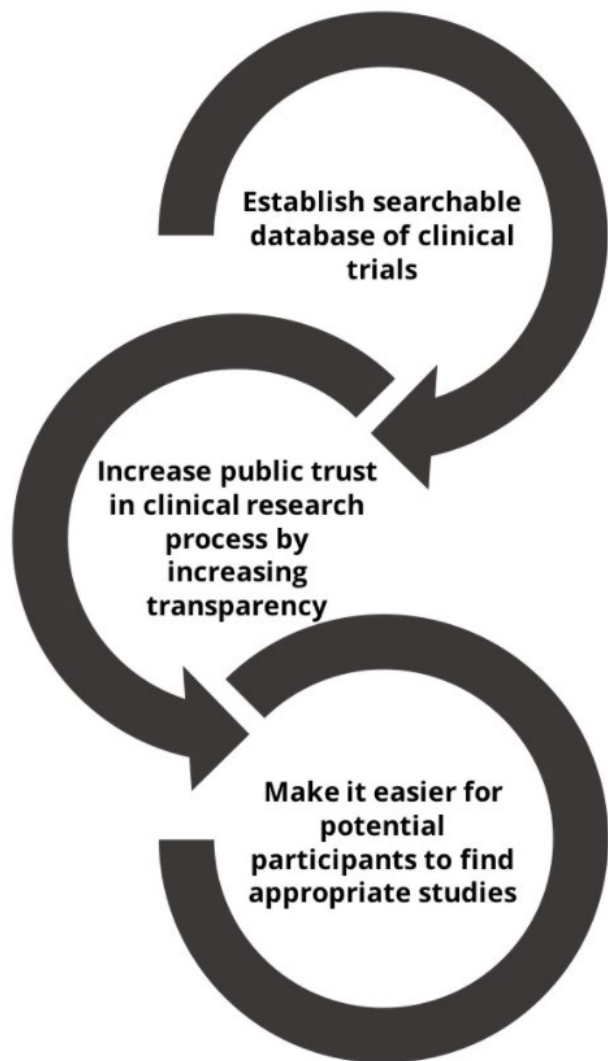
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What is clinicaltrials.gov?

- It is a resource that provides **access to information** on **clinical trials** studying a **wide range of diseases, conditions and interventions**.
- Studies listed in the database are conducted in all 50 States and in 220 countries.
- Each [ClinicalTrials.gov](https://clinicaltrials.gov) record includes **summary information about studies such as:**
 - **Study design and Intervention**
 - **Disease** or condition
 - Requirements for participation (**eligibility criteria**)
 - **Locations and Contact information**
 - Some records may include **outcomes of the study**

Summary of requirements:

Entity	Registration	Results Reporting	Penalties
<u>Health and Human Services</u> (HHS)	Within 21 days of enrollment	Within 365 days of primary completion date for ACTs	<ul style="list-style-type: none"> \$12,316/study/day Criminal proceedings Loss of grant funding
<u>National Institutes of Health</u> (NIH)	Within 21 days of enrollment	Within 365 days of primary completion date for clinical trials receiving NIH funding	Loss of grant funding (to include the institution)
<u>National Cancer Institute</u> (NCI)	Within 21 days of enrollment	Within 365 days of primary completion date of NCI-supported clinical trials (in a peer-reviewed journal and/or ClinicalTrials.gov)	Loss of grant funding
<u>Veterans Health Administration</u> (VHA)	Prior to release of funding. Prior to enrollment	Within 365 days of primary completion date	Loss of grant funding

Source: [Clinicaltrials.gov](https://clinicaltrials.gov) enforcement: an update. Anthony Keys. January 18, 2022

Summary of requirements:

Entity	Registration	Results Reporting	Penalties
<u>Centers for Medicare & Medicaid Services</u> (CMS)	All qualifying clinical trials	Study-specific	<ul style="list-style-type: none"> Coverage denial Costs and fraud investigations
<u>Patient-Centered Outcomes Research Institute</u> (PCORI)	All Clinical studies (including observational)	Expected of all PCORI Clinical studies – 500 word abstract published on PCORI website	<ul style="list-style-type: none"> Loss of grant funding
International Committee of Medical Journal Editors (ICMJE)	Prior to enrollment		Ineligibility to publish
<u>Department of Defense</u> (DoD)	Prior to enrollment. Prior to release of funding.	Study-specific	<ul style="list-style-type: none"> \$12,103/study/day Withholding or recovery of award funds

Source: Clinicaltrials.gov enforcement: an update. Anthony Keys. January 18, 2022

Registration may be required if one (or more) of the following is true:

1. The study is **funded by the National Institutes of Health** (NIH) **AND** meets the **NIH definition** of a clinical trial
2. The study involves **drugs, devices, or biologics** that are **regulated by the Food and Drug Administration** (FDA)
3. There is a plan to **publish the results in a medical journal** AND the study meets the International Committee of Medical Journal Editors (**ICMJE**) **definition of a clinical trial**
4. If your clinical trial will bill routine costs to **Medicare**, the study must be registered on ClinicalTrials.gov
5. If you have a clinical trial that includes a drug that available via **expanded access**.
6. If your **clinical trial receives funding** from **Department of Defense** (check with program Officer), **PCORI**, **National Cancer Institute**, **Veterans Affairs**



NIH funded clinical trials are required to be registered:

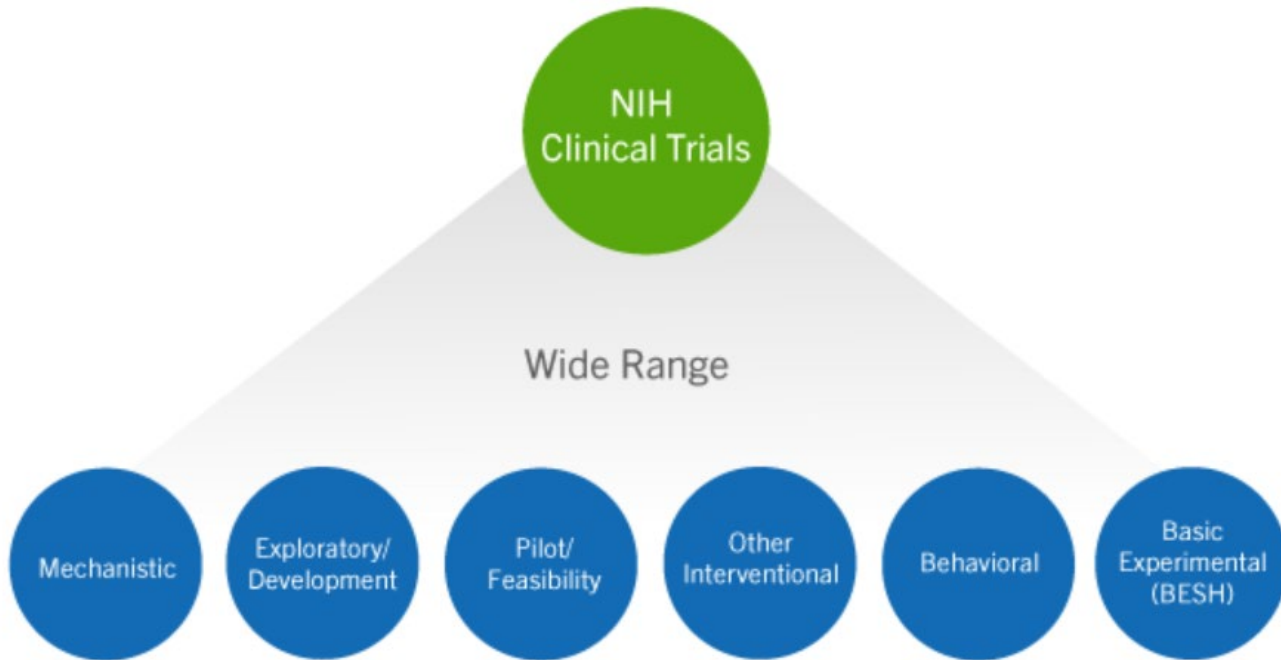
- If your study is NIH funded and meets the NIH definition of a clinical trial, then **clinicaltrials.gov registration** is required.
- For NIH funded research, use the following four questions to determine the **difference** between a **clinical study** and a **clinical trial**:
 - Does the study involve **human participants**?
 - Are the participants **prospectively assigned** to one or more interventions?
 - Is the study designed to **evaluate the effect of the intervention** on the participants?
 - Is the effect being evaluated a **health-related biomedical** or **behavioral outcome**?
- If the answers to ALL 4 questions are “yes”, your study meets the NIH definition of a clinical trial.

NIH Definition of an “INTERVENTION”:

An "intervention" is defined 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.

Examples include:

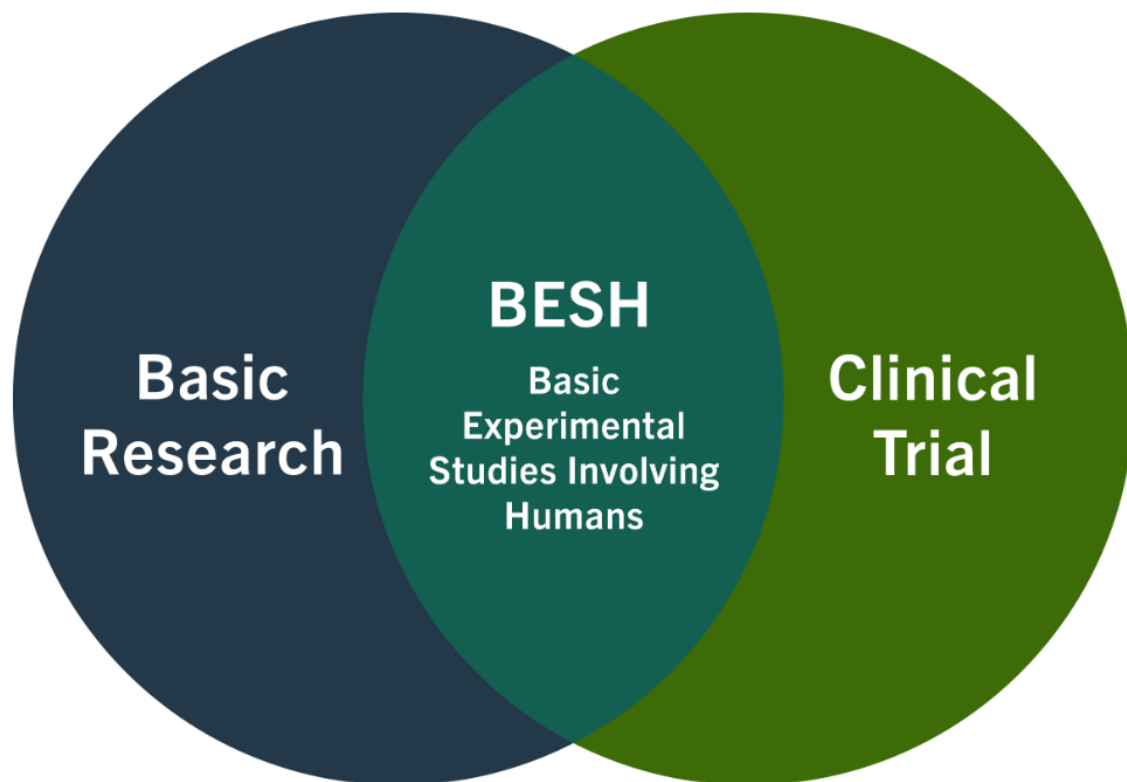
- drugs/small molecules/compounds;
- biologics; devices;
- procedures (e.g., surgical techniques);
- delivery systems (e.g., telemedicine, face-to-face interviews);
- strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits);
- treatment strategies; prevention strategies; and diagnostic strategies.



This includes

- studies with **healthy participants**
- **Phase 1** trials of FDA-regulated drugs and biological products
- **Small feasibility studies** of FDA regulated device products
- studies with **no comparison group** (placebo or control)
- studies designed to assess the pharmacokinetics / safety of an investigational drug
- Studies where only **one aim or sub-aim meets the clinical trial definition.**

Some NIH funded Basic experimental studies involving humans are also required to be registered:



- **Basic experimental studies involving humans (BESH)** are studies that meet both the definition of basic research and the NIH definition of a clinical trial.
- Basic research uses a range of probes or **experimental manipulations to perturb a physiological process** (including cognitive and perceptual processes).
- **NIH published clinical trial case studies** with examples of BESH (**cases 9, 14, 40 & 41**).
- ***Example:** healthy volunteers randomized to different durations of sleep deprivation where the dependent variable is stress hormone levels.*



Registration is also required if your study meets the **DHHS definition of an Applicable Clinical Trial (ACT)**. These include:

- **Controlled clinical investigations** (other than phase 1 investigations) of any **U.S. Food and Drug Administration (FDA)-regulated drug or biological** product for any disease or condition
- It also includes certain studies of **FDA-regulated medical devices**, and **FDA-required pediatric post market surveillances** of a device product



The Food and Drug Administration Amendments Act of 2007 (**FDAAA**) established legal requirements for **sponsors and designated principal investigators** (i.e., responsible parties) **to report specified clinical trial information** for certain ACT's to [ClinicalTrials.gov](https://clinicaltrials.gov).

The requirements are designed to

- provide potential participants with **information about trials of interest**,
- reduce publication bias,
- **help institutional review boards (IRBs)** determine the **appropriateness of a research study**,
- and promote more efficient allocation of research funds.

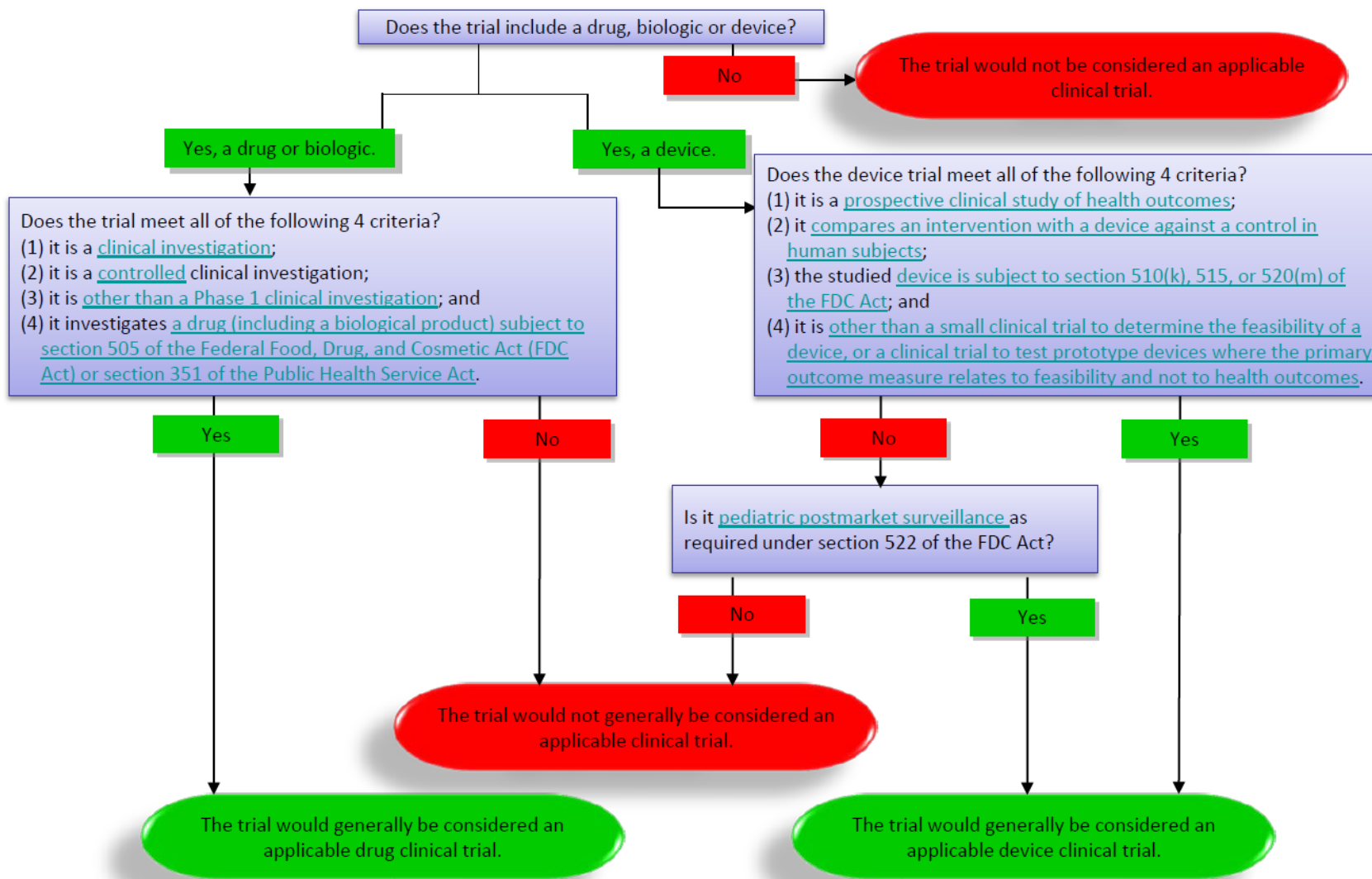
Question	Yes	No
1. Is the study interventional (a clinical trial)? <i>Study Type data element is "Interventional"</i>	<input type="checkbox"/>	<input type="checkbox"/>
2. Do ANY of the following apply (is the answer "Yes" to <u>at least one</u> of the following sub-questions: 2a, 2b, OR 2c)?	<input type="checkbox"/>	<input type="checkbox"/>
a. Is at least one study facility located in the United States or a U.S. territory? <i>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.</i>		
b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)? <i>U.S. Food and Drug Administration IND or IDE Number data element is "Yes."</i>		
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? <i>Product Manufactured in and Exported from the U.S. data element is "Yes."</i>		
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)? <i>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."</i>	<input type="checkbox"/>	<input type="checkbox"/>
4. Is the study <u>other than</u> a Phase 1 trial of a drug and/or biological product or is the study <u>other than</u> a device feasibility study? <i>For drug product trials, Study Phase data element is NOT "Phase 1" and for device product trials, Primary Purpose is NOT "Device Feasibility."</i>	<input type="checkbox"/>	<input type="checkbox"/>

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.

Researchers can use the following tools to determine if their trial meets the DHHS definition of an ACT:

- [Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial](#)
- [Identifying an ACT under FDAAA \(flowchart\)](#)

Identifying an Applicable clinical trial:



ACT – important definitions:

Is the study interventional (a clinical trial)?

- 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**. [Source: 42 CFR 11.10(a); 81 FR 65140-41]

Does the study evaluate at least one U.S. FDA-regulated drug, biological, or device product?

- A device product is considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act if any of the **following is required before it may be legally marketed in the United States**: (1) a finding of substantial equivalence under section **510(k)** of the FD&C Act, (2) an order under section 515 of the FD&C Act approving a premarket approval application (**PMA**) for the device product, or (3) an **HDE** under section 520(m) of the FD&C Act.
- Device products that are considered to be subject to section 510(k), 515, or 520(m) of the FD&C Act include **significant risk devices** for which approval of an IDE is required, **non-significant risk devices** that are considered to have an approved IDE in accordance with 21 CFR 812.2(b), or device products that are exempt from the submission requirements of 21 CFR part 812. [Source: 81 FR 65012]

Registration Requirements per International Committee of Medical Journal Editors (ICMJE):



- In 2005, the ICMJE defined trials that must be registered in order to be considered for publication in journals that adhere to ICMJE standards.
 - “we will consider a trial for publication only if it has been registered before the enrollment of the first patient. This policy applies to trials that start recruiting on or after July 1, 2005. Because many ongoing trials were not registered at inception, we will consider for publication ongoing trials that are registered before September 13, 2005. ”
- In 2007, the **ICMJE expanded the definition of trials that must be registered.**
- Many journals (not limited to medical journals) have adopted the registration policy.



ICMJE DEFINITION OF CLINICAL TRIAL



In June 2007 the ICMJE adopted the WHO's definition of clinical trial: "**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.**"

- with or without concurrent comparison or control groups,
- **Health-related interventions** are those used to modify a biomedical or health-related outcome; examples include drugs, **surgical procedures**, devices, **behavioral treatments**, **educational programs**, dietary interventions, quality improvement interventions, and process-of-care changes.
- **Health outcomes** are any **biomedical or health-related measures** obtained in patients or participants, including pharmacokinetic measures and adverse events.
- Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

The ICMJE...

- ...encourages registration of research with **non-trial designs (e.g., observational studies)**
- ...journals will consider trials beginning on or after July 1, 2005 **only if registration occurred before the first patient was enrolled ("prospective registration")**.
- ...does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.
- An acceptable registry must include the minimum [24-item trial registration data set](#) at the time of registration.

****Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal****

Required for Medicare Billing:

If your study will bill routine costs to Medicare or any other insurer, the study must be registered on ClinicalTrials.gov to obtain the NCT#.

- A Qualifying Clinical Trial (QCT) is a trial that meets the requirements set forth in the Clinical Trial Policy (NCD 310.1) by the Centers for Medicare and Medicaid Service (CMS).
- Once a trial has been determined to be a QCT, the routine costs associated with it are billable to and reimbursable by Medicare and third-party payors.
- **CMS requires** a clinical trial identifier (NCT#) be reported on all billing claims for items/ services related to a qualifying clinical trial.

Expanded access use:

- Under FDA regulations (21 CFR 312.300), **expanded access** allows for the use of **unapproved drugs and biologics outside of a clinical trial** for **patients with serious diseases or conditions** when there is **no satisfactory alternative** therapy to treat the patient's disease or condition. This is sometimes referred to as compassionate use or treatment use.
- [Expanded access records](#) which describe the **procedure for obtaining** an experimental drug or device outside of a clinical trial are **required** to be **submitted to the ClinicalTrials.gov database**.

Other Funding Entities Requiring CT.gov Registration:

Registration may be required if your **clinical trial receives funding** from:

- Department of Defense (check with program Officer)
- PCORI
- National Cancer Institute
- Veterans Affairs

Why Do I Need to Register My Trial and Submit Results to ClinicalTrials.gov? here are just some of the reasons...

- **Required by Law:** [Section 801 of the Food and Drug Administration Amendments Act \(FDAAA 801\)](#) requires responsible parties to register clinical trials and submit summary results to ClinicalTrials.gov.
- **Required for Journal Publication:** The International Committee of Medical Journal Editors (ICMJE) [requires trial registration](#) as a condition of the publication of research results generated by a clinical trial.
- **All NIH-funded clinical trials** are expected to register and submit results information to [Clinicaltrials.gov](#), as per the ["NIH Policy on Dissemination of NIH-Funded Clinical Trial Information"](#) for competing applications and contract proposals.
- [WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects](#): "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject" (para. 35).

What is the penalty for non-compliance?



Under NIH Policy: Noncompliance with the terms and conditions of the NIH award may provide a basis for enforcement actions, such as withholding current and future funding [45 CFR 75.371, 42 CFR 11.66]

Under Final Rule, responsible parties 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**. [2016 NEJM article]

➤ **Case in point:**

On 28 April 2021, the FDA issued its first Notice of Noncompliance to **Georgia-based Accutis** who failed to submit required summary results information. The company could be “subject to a civil monetary penalty of **\$10,000 for each day of the violation**” until the noncompliance is corrected.

ICMJE: authors failing to prospectively register a trial risk its **inadmissibility to journals** following the ICMJE’s trial registration policy.

My study does not meet the CT.gov registration criteria...but can I register anyway?

In **2015**: **19,170** clinical trials were registered. **7,400** were applicable clinical trials, **the remainder 11,770 trials, can be considered voluntary** or to not fall under the rule. Of these, 526 were NIH funded. This leaves an estimated **11,244 trials** that do not fall under either the rule or the NIH policy!

DHHS expects that these clinical trials will:

- submit the **same clinical trial registration information** as is submitted for applicable clinical trials that are subject to the rule.
 - expects that information submitted for such clinical trials will be **updated as frequently** as information for applicable clinical trials that are subject to the rule.
 - **Estimated annual burden of 269,856 hours (almost 90,000 hours initial registration, rest from updates)**
- Voluntary registration places a burden on the responsible party to comply with all registration and update requirements. Any ongoing non-compliance with these requirements on the part of the responsible party.

Who is responsible for registering and Submitting Results to ClinicalTrials.gov?

- The “Responsible Party” refers to the entity or individual who is **responsible for registering** a trial on ClinicalTrials.gov.
- The Responsible Party is responsible for the initial release of the record, all **future updates** and ensuring the trial registration **stays accurate and up-to-date**.
- For studies registered by UCI, the PI serves as the responsible party if they meet all the following criteria:
 1. They are responsible for **conducting the clinical trial**.
 2. They have **access to and control over the data**
 3. They have the **right to publish the results** of the trial
 4. They can **meet all the requirements for the submission** of clinical trial information.



Submission process:



1. **A ClinicalTrials.gov staff member** will review the study record after it is submitted and before it is published on ClinicalTrials.gov.
2. The **review process may take up to a few days**. Ensuring that the record is consistent with the ClinicalTrials.gov Protocol Review Criteria (PDF) before releasing it will expedite publication on the site.
3. After it is accepted by review staff for publication, the record, including its **NCT Number, will be available on ClinicalTrials.gov within 2-5 business days**.

Obligations of the Responsible Party once registered

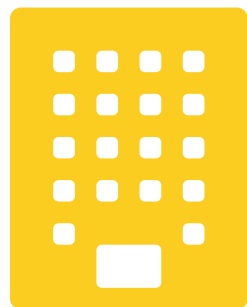


Data Element	Deadline for Updating (i.e., not later than the specified date)
Study Start Date	30 calendar days after the first subject is enrolled (if the first human subject was not enrolled at the time of registration).
Intervention Name(s)	30 calendar days after a nonproprietary name is established.
Availability of Expanded Access	30 calendar days after expanded access becomes available (if available after registration); and 30 calendar days after an NCT number is assigned to a newly created expanded access record. [1]
Expanded Access Status	30 calendar days after a change in the availability of expanded access.
Expanded Access Type	30 calendar days after a change in the type(s) of available expanded access.
Overall Recruitment Status	30 calendar days after a change in overall recruitment status. [2]
Individual Site Status	30 calendar days after a change in status of any individual site.
Human Subjects Protection Review Board Status	30 calendar days after a change in status.
Primary Completion Date	30 calendar days after the clinical trial reaches its actual primary completion date.
Enrollment	At the time the primary completion date is changed to "actual," the actual number of participants enrolled must be submitted.
Study Completion Date	30 calendar days after the clinical trial reaches its actual study completion date.
Responsible Party, by Official Title	30 calendar days after a change in the responsible party or the official title of the responsible party.
Responsible Party Contact Information	30 calendar days after a change in the responsible party or the contact information for the responsible party.
Device Product Not Approved or Cleared by U.S. FDA	15 calendar days after a change in approval or clearance status has occurred.
Device Product Not Approved or Cleared by U.S. FDA	15 calendar days after a change in approval or clearance status has occurred.
Record Verification Date	Any time the responsible party reviews the complete set of submitted clinical trial information for accuracy and not less than every 12 months, even if no other updated information is submitted at that time.

Source: <https://clinicaltrials.gov/ct2/manage-recs/faq>

NEW: Uploading the Consent Form per revised Common Rule

Effective January 21, 2019. Important considerations regarding the uploading of the informed consent form:



Applies to clinical trials **conducted or supported by a Federal department or agency** using the **Common Rule (e.g., NIH, DOD, DVA)**



The consent form must have been **used in enrolling participants**



Should be uploaded **no later than 60 days after the last study visit** by any subject, as required by the protocol



Must be uploaded to either **ClinicalTrials.gov** or a docket folder on **Regulations.gov**

[Source: §46.116 General requirements for informed consent.]