Hartford HealthCare

Clinical Trials Registration

On September 27, 2007 Congress enacted U.S. Public Law 110-85 (also known as H.R. 3580, or Food and Drug Administration Amendments Act of 2007, FDAAA 801). This act mandates the expansion of www.ClinicalTrials.gov, expands the required submission elements and establishes penalties for not listing a trial. In addition, conforming amendments to the Federal Food, Drug and Cosmetic (FD&C) Act are now included. The regulation became effective on January 18, 2017, and responsible parties have been required to be in compliance starting April 18, 2017.

All **Applicable Clinical Trials** must be registered as required by FDA regulation.

The FDA requirements are in addition to the 2005 policy established by the International Committee of Medical Journal Editors (ICMJE) requiring the entry of clinical trials in a public registry prior to subject enrollment as a condition of consideration for publication of the trial results. The FDA Final Rule for Clinical Trials Registration (42 CFR Part 11) clarifies and expand the regulatory requirements and procedures for submitting registration and results information for certain trials to ClinicalTrials.gov, in accordance with FDAAA 801.

HELPFUL DEFINITIONS:

According to Public Law 110-85 (Title VIII; Sec. 801), "**Applicable Drug Clinical Trial**" means "a controlled clinical investigation, other than a Phase I clinical investigation, of a drug subject to section 505 ("new drugs") of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act [PHS Act]".

Clinical Investigation (per 21 CFR 312.3) means “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. [For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.]"

According to Public Law 110-85 (Title VIII; Sec. 801), "**Applicable Device Clinical Trial**" means "a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to test prototype devices), or a clinical trial to test prototype devices where the primary outcome measures relates to feasibility and not to health outcomes." These studies also include the FDA-required pediatric postmarket surveillances of a device product.

According to Public Law 110-85 (Title VIII; Sec. 801), "**Responsible Party**" means "(1) the sponsor of the clinical trial (as defined in 21 CFR 50.3) OR (2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the PI 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 trail information."

In General, the Responsible Party must register an Applicable Clinical Trial within 21 days after the first patient is enrolled. Please note that some journals will not accept subjects enrolled prior to registration.

> *EXCEPTION:* If a trial was initiated before 9/27/07 and enrollment and patient involvement was complete by 12/26/07, the trial does not have to be registered.

FREQUENTLY ASKED QUESTIONS:

Who is responsible for registering a study?

The FDA regulations require the responsible party to register applicable clinical trials. The responsible party is the sponsor of the clinical trial, meaning the person who initiates a clinical investigation.

- For investigator-initiated trials, the lead principal investigator responsible for initiating, conducting and coordinating the overall clinical trial is responsible for registration.
- For sponsor-initiated (industry-sponsored) trials the sponsor is responsible for registration.
- For trials sponsored or funded wholly or in part by the NIH the grantee (PI) is responsible for registration.
- For trials associated with Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications with the FDA the IND/IDE holder is responsible for registration.
- The sponsor, grantee, contractor, or awardee may designate the principal investigator of a clinical trial as the responsible party, provided that 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 for submitting information under the law.

If unclear who is responsible 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. Due to length of some studies, the party responsible for registration should not be planning to leave the institution (other endeavor, retirement, etc.) for the duration of the trial.

How do I register a trial on ClinicalTrials.gov?

- Search ClinicalTrials.gov to ensure that the trial is not already listed. NIH-sponsored clinical trials and many industry-sponsored trials have already been registered on this site. If the trial is not listed, continue. It is suggested to search using at least two criteria, e.g., title and disease/diagnosis.

- Establish a user account with the ClinicalTrials.gov Protocol Registration System (PRS) by sending an e-mail message to Hartford Hospital's PRS administrator, Cherie Bilbie at cherie.bilbie@hhchealth.org. The subject line of the e-mail should state "ClinicalTrials.gov Protocol Registration" and the body of the message should contain your **name**, **telephone number**, and **HHC email address**.

- Within 2 business days, you will receive an e-mail message from ClinicalTrials.gov containing your login name and temporary password.

- Once you have received your login information, register the trial. This process will take approximately 1-2 hours, and it will be helpful to have the protocol, informed consent document, and IRB approval (if available) on hand. IRB approval is not required to register a trial. Note that this system offers the option to save data if you do not have time to complete the entire process.

- To begin the registration process, go to the ClinicalTrials.gov registration website [https://register.clinicaltrials.gov/]. Complete the login fields. In the "**Organization**" field, enter **HartfordH**.

- The "Main Menu" page will appear. The "User Account" link provides information on changing your temporary password, and this should be done as soon as possible. This link also has a helpful "User's Guide."

- To complete the protocol template, begin from the "Main Menu" page, go to "Protocol Record" and select "Create." You can copy and paste information from the protocol into the data fields. A list of all the variables you will be asked to provide can be found at http://prsinfo.clinicaltrials.gov/definitions.html and a guided tour is available at http://prsinfo.clinicaltrials.gov/title.html .

- Some suggestions for completing certain items that you might not have available are:

  Unique protocol ID: The Reference # found on the Research Application is recommended. IRB approval is not required to register a trial.

  Secondary IDs: The grant number, funding agency number or other funding source number is recommended.

  Board Name (*Full name of the approving human subjects review board*): Hartford HealthCare Institutional Review Board

  Board Affiliation (*Official name of organizational affiliation of the approving human subjects review board*): Hartford HealthCare

  Board Contact (*Contact information for the human subjects review board*):
  Name: Cherie Bilbie
  Phone: 860-972-0088
  Email: Cherie.bilbie@hhchealth.org
  Address: Dept. of Research Administration, 80 Seymour Street, PO Box 5037, Hartford, CT 06102-5037

  Oversight Authorities: should always include "**United States: Institutional Review Board**"; other oversight authorities such as the FDA may also apply depending on the clinical trial

- When the template is complete, hit "Submit." The template will be forwarded to the Institution's PRS administrator who will review it and release the approved content to ClinicalTrials.gov

- Comments on registration must be responded to within 15 calendar days.

****Information should be reviewed and updated as needed every 6 months or more frequently if changes occur, but must be verified at least annually.**

What is the URL for the ClinicalTrials.gov registration site?

The URL for the registration site is: https://register.clinicaltrials.gov/

Which studies are required by the FDA regulation to be registered?

Registration is required for any research study that:

- Prospectively assigns human subjects to intervention and at least one concurrent control or comparison groups AND
- Uses a drug, biologic, or device as the intervention or control/comparison AND
- Studies the safety, efficacy or cause-and-effect relationship between an intervention and a health outcome
- Pediatric post-market surveillance required by FDA
- Trial is conducted under an FDA IND/IDE application
- Trial involves a drug, biologic, or device that is manufactured in the U.S. or its territories and exported for research

- For additional information on the meaning of Applicable Clinical Trial (ACT), see the criteria specified in 23 CFR 11.22(b).It is acceptable to register a trial that does not meet one of these requirements, but not necessary.

The FDA registration requirement does not apply to:

- The use of FDA approved, marketed products used in the course of medical practice
- Phase I clinical investigations of drugs or biologics
- Small clinical trials to determine the feasibility of a device or clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes
- Purely observational studies, meaning those studies where the assignment of the intervention is not at the discretion of the investigator.

What are the International Committee of Medical Journal Editors requirements for registering clinical trials?

Investigators and sponsors are also encouraged to register all clinical trials to ensure they meet the publication requirements of the International Committee of Medical Journal Editors (ICMJE). To promote transparency of the clinical trial process, the International Committee of Medical Journal Editors (ICMJE) established a policy in 2005 requiring the entry of clinical trials in a public registry prior to subject enrollment as a condition of consideration for publication of the trial results. The ICMJE requires any research project that prospectively assigns human subjects to intervention and at least one concurrent control or comparison group to study the association between a medical intervention and a health outcome should be registered. Studies designed for other purposes such as evaluation of pharmacokinetics or toxicity (e.g. phase I trials) are not required to be registered. Medical intervention is defined broadly and includes any intervention used to modify a health outcome, including drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

What are the NIH Requirements for ClinicalTrials.gov Registration Information in Applications and Progress Reports?

On September 16, 2016, the NIH published the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information in NIH Guide Notice NOT-OD-16-149. This guide is complementary to the 42 CFR Part 11 regulation. Investigators and sponsors must ensure that applicable drug, biologic and device trials are registered within 21 days of enrollment of the first subject and preferably before first subject enrollment. The legislation also requires applications or progress reports for any clinical trials required to be registered which are funded in whole or in part by a grant from any agency of the Department of Health and Human Services to contain specific information registration in ClinicalTrials.gov. Additionally, as part of their applications of proposals, applicants seeking NIH funding will be required to submit a plan for the dissemination of NIH-funded clinical trial information.

NIH Policy on Clinical Studies

- Definition of a Clinical Trial: A research study in which one or more human subjects or prospectively assigned to one or more interventions (which may

include placebo or other control) to evaluate the effects of those intervention of health-related biomedical *or behavioral outcomes*.
- All NIH-funded clinical trials regardless of study phase, type of intervention (even if not an ACT) including behavioral interventions must register.

How do the FDA registration requirements affect NIH funded studies?

Competing renewal applications that include studies that are required to be registered must include as part of the Human Subjects Section of the Research Plan the following items:

- A statement that "This application includes a trial which requires registration in ClinicalTrials.gov,"
- The National Clinical Trial (NCT) number (i.e. the ClinicalTrials.gov number)
- Brief Title as listed in ClinicalTrials.gov, and
- The name of the individual or entity responsible for registering the study (responsible party) for each study being conducted under the application. (As grantee, Hartford HealthCare designates the lead investigator of the trial as the responsible party.)

If the application does not include studies that are required to be registered the Human Subjects Section of the Research Plan should include a statement that "This application does not include a trial which requires registration in ClinicalTrials.gov." These requirements apply to all competing applications submitted to the NIH on or after January 25, 2008.

New applications that include studies that are required to be registered must include as part of the Human Subjects Section of the Research Plan a statement that "This application includes a trial which requires registration in ClinicalTrials.gov." The study would then need to be registered and the National Clinical Trial (NCT) number, Brief Title as listed in ClinicalTrials.gov and the individual or entity responsible for registering the study (responsible party) for each study being conducted under the application as part of the Just-In-Time (JIT) information. If a New application does not include studies that are required to be registered the Human Subjects Section of the Research Plan should include a statement that "This application does not include a trial which requires registration in ClinicalTrials.gov."

Non-competing progress reports that include studies that are required to be registered must include as part of the Human Subjects Section of the Progress Report the following items:

- A statement that "This application includes a trial which requires registration in ClinicalTrials.gov,"
- The National Clinical Trial (NCT) number (i.e. the ClinicalTrials.gov number),
- Brief Title as listed in ClinicalTrials.gov and,
- The name of the individual or entity responsible for registering the study (responsible party) for each study being conducted under the application. (As grantee, Hartford HealthCare designates the lead investigator of the trial as the responsible party.)

If the application does not include studies that are required to be registered the Human Subjects Section of the Research Plan should include a statement that "This application does not include a trial which requires registration in ClinicalTrials.gov." These requirements apply to all non-competing progress reports with budget start dates of April 1, 2008 or later (applications due on or after February 1, 2008).

Do the FDA regulations have any special requirements for IND, IDE or BLA studies?

- Studies conducted under an IND (investigational new drug) or IDE (investigational device exemption) must include in the informed consent documents and the informed consent process a statement that clinical trial information for the study has been or will be submitted for inclusion in ClinicalTrials.gov as required by FDA regulations.
- A certification must accompany human drug, biological, and device product submissions made to FDA. At the time of submission of an IND, IDE or BLA (biologic license application) application or submission of a report, amendment, supplement or resubmission, such application or submission must be accompanied by a certification that all applicable requirements related to clinical trial registration have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) numbers.
- The official certification form, Form FDA 3674 entitled "Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank", is available on FDA's Web site.
- For sponsor held INDs, IDEs and BLAs the sponsor must provide the certification. For investigator held INDs, IDEs and BLAs the individual holding the IND, IDE or BLA must provide the certification.

What are my responsibilities once I register a trial?

You are responsible for ensuring that the information is complete, accurate and updated. This includes reviewing the listing and making necessary changes ***every 6 months*** or more frequently if significant changes occur **but at least annually**. You are also responsible for noting when enrollment is closed.

- The study record must be updated within 30 days with regard to completion dates or recruitment status.
- Results are due 365 days from primary completion date (extensions for good cause may apply)
- Submission of full protocol and statistical analysis plan is required with submission of results information.
- The informed consent form may need to also be uploaded to the clinical trial submission.
- If an ICF has been submitted/approved prior to attaining an NCT#, a modification should be submitted in iRIS with the NCT# added to the ICF as soon as it is acquired.

Potential Legal Consequences of Non-compliance

- The Final Rule 42 CFR Part 11.66 describes possible civil or criminal judicial actions.
- Civil monetary penalties up to $12,103 per study, per day for any issue of non-compliance are possible.
- Loss of grant funding or termination of funding may apply for NIH-funded studies.

Where can I find more information from the NIH about the requirement to register clinical trials?

The NIH has posted information on clinical trials registration at:
http://grants.nih.gov/ClinicalTrials_fdaaa/

Who can I contact at Hartford HealthCare for more information about the requirements to register clinical trials?

Contact Cherie Bilbie by email (Cherie.bilbie@hhchealth.org) or phone (860-972-0088) to establish a user account to register a study with the ClinicalTrials.gov Protocol Registration System.

Are there other sources of information about clinical trial registration?

ClinicalTrials.gov: http://clinicaltrials.gov/

https://clinicaltrials.gov/ct2/manage-recs/fdaaa

International Committee of Medical Journal Editors:
http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Center for Drug Evaluation and Research; US Food and Drug Administration. Guidance for industry information program on clinical trials for serious or life-threatening diseases and conditions. Available at: https://www.fda.gov/media/71927/download

WHO International Clinical Trials Registry Platform (ICTRP):
http://www.who.int/ictrp/en/

National Library of Science and Medicine ClinicalTrials.gov Questions
https://clinicaltrials.gov/ct2/help/for-researcher

Final Rule (42 CFR Part 11.66)
https://www.govinfo.gov/content/pkg/FR-2019-11-05/pdf/2019-23955.pdf