

The Food and Drug Administration Amendments Act (FDAAA) of 2007 (US Public Law 110-85) expanded the scope of registration of clinical trials at ClinicalTrials.gov, increased the amount of information that must be provided at the time of registration, required the inclusion of trials results, and imposed penalties for non-compliance.

Previously, the Food and Drug Administration Modernization Act (FDAMA) of 1997, which established ClinicalTrials.gov, mandated the registration of FDA-regulated efficacy drug trials for serious or life-threatening diseases or conditions.

As of 2005, most medical journals, including the International Committee of Medical Journal Editors (ICMJE), require as a condition of consideration for publication, the prospective registration of certain clinical trials in a public trials registry. Failing to register makes the results of the trial ineligible for publication in the ICMJE member journals. ICMJE member publications include:

- Journal of the American Medical Association (JAMA)
- New England Journal of Medicine (NEJM)
- Annals of Internal Medicine
- The Lancet
- Canadian Medical Association Journal (CMAJ)
- The New Zealand Medical Journal
- The Medical Journal of Australia
- Norwegian Medical Journal
- Croatian Medical Journal
- Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine)
- Journal of the Danish Medical Association

Which studies must be registered?

The FDAAA of 2007 requires the registration of the following types of studies:

- Controlled, clinical investigations of drugs and biologics subject to FDA regulation, other than Phase I trials; and
- Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, but including pediatric postmarket surveillance of devices ordered under section 522 of the Federal Food, Drug and Cosmetic Act.

The ICMJE policy goes beyond the FDAAA requirements by promoting public access to all "clinically directive" trials -- trials that test a clinical hypothesis about health outcomes. In accordance with ICMJE policy, any clinical trial that "prospectively

assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome", should be registered. Most Phase 2 and all Phase 3 trials are subject to this ICMJE registration policy.

- A "trial" must have at least one prospectively assigned concurrent control or comparison group in order to trigger the requirement for registration.
- A "medical intervention" means any intervention used to modify a health outcome, including studies on drugs, surgical procedures, devices, behavioral treatments, process-of-care changes and the like.

Studies that are designed for other purposes (retrospective records review, pharmacokinetics studies, assessment of major unknown toxicity, and other Phase 1 trials) are generally exempt from FDAAA, FDAMA and ICMJE requirements.

Who is responsible for registering a trial?

The FDAAA defines the entity responsible for registering the trial as the "responsible party." The responsible party is defined as:

- The sponsor of the clinical trial (as defined in 21 CFR 50.3)
- The Principal Investigator of the clinical if so designated by a sponsor, grantee, contractor, or awardee.

Investigator-initiated: For investigator-initiated trials, the UIC PI should register each clinical trial affected by the FDAAA of 2007 and ICMJE policy.

Multi-site: For multi-site trials, the lead sponsor/site should register the trial. Likewise for IND or IDE studies, the IND or IDE holder should be responsible for registering the clinical trial. It is important that each UIC PI coordinates the registration process with their sponsor or lead sponsor/site in multi-site trials to ensure that the necessary registration has been completed and to avoid duplicate registrations.

NIH-sponsored: For NIH-sponsored extramural research, where there is no IND or IDE holder, the funding recipient may be the "responsible party." NIH would not be the responsible party.

Before PI's register a sponsored trial, they should search the ClinicalTrial.gov site to be sure that the trial has not already been registered. Investigators are also encouraged to consult with the Office of Research Services for questions regarding their responsibility to register a study as negotiated through a clinical trial agreement, grant or contract.

When must a trial be registered?

For ICMJE publication:

Note: ICMJE requirement is more stringent than FDAAA requirement regarding registration timing.

- Prior to the enrollment of the first subject

For FDAAA compliance:

- Trials initiated after 9/27/2007, or trials that **are** “ongoing” as of 12/26/2007 must be registered in full by: the later of 12/26/2007 or 21 days after the first patient is enrolled.
- Trials that **were** “ongoing” as of 9/27/2007 and do **not** involve a “serious or life threatening disease or condition,” must be registered by 9/27/2008.
- Trials that **were** “ongoing” as of 9/27/2007, **do** involve a “serious or life threatening disease or condition,” and are completed by 12/26/2007, are not subject to the FDAAA requirements, though they are subject to pre-existing FDAMA requirements.

“Ongoing” in this context means a trial has enrolled one or more subjects, but has not examined the final subject or provided the final subject an intervention for the purposes of final collection of data for the primary outcome as of 9/27/2007.

Once registered, the related information should be updated during the course of the trial. In multi-site trials, the UIC investigator should work collaboratively with sponsors and principal investigators to avoid duplication of efforts.

Where should a clinical trial be registered?

The trial should be registered through the ClinicalTrials.gov Protocol Registration System (PRS). The ClinicalTrials.gov PRS is a service of the U.S. National Institutes of Health (NIH), provided through its National Library of Medicine (NLM) that meets the FDAMA, FDAA and ICMJE requirements. Information regarding the PRS site can be found at <http://prsinfo.clinicaltrials.gov/fdaaa.html>.

How does a responsible party register his/her trial?

If a UIC PI is considered to be or designated as the responsible party, the investigator should proceed to the ClinicalTrials.gov PRS site at <http://prsinfo.clinicaltrials.gov> to register the trial. Under “Account Application Process,” choose “Apply for an individual account” (instructions are provided below). Alternatively, a department or unit may establish an organizational account with an individual identified as the account’s PRS Administrator. Additional UIC specific registration information can be found at the end of this policy.

The ClinicalTrials.gov PRS site includes a guided tour, definitions, frequently asked questions, and a list of the data elements needed for registration. If you have questions or encounter problems in the registration process, contact register@clinicaltrials.gov.

Does the registration listing need IRB approval?

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.

Direct advertising for study subjects, however, does require prospective IRB approval because it is considered to be part of the informed consent and subject selection process.

Clinical trial registration should not be construed as a requirement for IRB approval.

For further information, refer to the following guidance:

- OHRP -<http://www.hhs.gov/ohrp/policy/clinicaltrials.html>
- FDA -<http://www.fda.gov/oc/ohrt/irbs/toc4.html>

What happens if you do not register your clinical trial?

The FDAAA of 2007 imposes penalties for failure to register or for providing false or misleading information about an applicable trial. These penalties include non-compliance notices from the FDA, civil monetary penalties up to \$10,000/day and for federally-funded trials, the withholding or recovery of grant funds.

Additionally, researchers who have not registered or have improperly registered their trials take the risk that their manuscripts may not be reviewed and/or accepted by ICMJE members and other medical journals.

What about submitting information regarding trial results?

The FDAAA requires the responsible party to report the “basic results” for all applicable clinical trials including:

- Phase II-IV interventional studies;
- Studies involving drugs, biologics, and medical devices regulated by the FDA;
- Studies with at least one site in the U.S. or conducted under an IND or IDE;
- Studies initiated after or on-going as of September 27, 2007.

When should results be posted?

Except as noted below, the FDAAA requires that results be submitted within 12 months of the *earlier* of the “estimated” trial completion date or the actual completion date. This is the date that the final subject was examined or received an intervention for the purposes of final collection of data for a primary outcome in accordance with the protocol or study termination (defined as Primary Completion Date in ClinicalTrials.gov).

The submission of results may be delayed for the following clinical trials:

- Trials of a drug or device for which the manufacturer is seeking initial approval for marketing (results must be submitted within 30 days of approval);
- Trials of a drug or device of a marketed agent for which the manufacturer has filed an application seeking approval of a new use studied in the trial;
- Trials for which a request “demonstrates good cause” as granted by the Director of NIH.

What type of results must be reported?

The type of results is divided into two different categories: scientific information and administrative information.

Scientific information includes participant flow; baseline and demographics characteristics; outcome measures and statistical analyses; and adverse events (optional prior to September 2009). Information regarding the “Basic Results” data definitions can be found at http://prsinfo.clinicaltrials.gov/results_definitions.html . Guidance documents are available relating to the basic results reporting including “helpful hints” and “common errors” - <http://prsinfo.clinicaltrials.gov/fdaaa.html> .

Administrative information includes point of contact information about the reported results and any agreements or limitations restricting results disclosure.

What adverse events must be reported?

The FDAAA (effective September 2009) requires the reporting of all serious and frequent adverse events.

Serious adverse events are reported in the following manner.

- Table of anticipated & unanticipated serious adverse events
- Grouped by organ system
- Number and frequency of event in each clinical trial arm

Frequent (other) adverse events are reported in the following manner.

- Table of anticipated & unanticipated adverse events
- Exceed a frequency of 5 percent within any trial arm
- Grouped by organ system
- Number and frequency of event in each trial arm

Instructions to Apply for an Individual Account Application

- On the ClinicalTrials.gov Protocol Registration System (PRS) home page (<http://prsinfo.clinicaltrials.gov/>), under “Account Application Process,” select “Apply for an individual account.”

- The “Getting a PRS Individual Account” page will open and ask six questions before starting the account application process. If you get to question 6, “Is your organization already registered with the PRS?” answer “no” and select “Apply for a PRS account”.
- The “Individual Account Application” page will open. First, read and accept/not accept the terms and conditions for submitting data to ClinicalTrials.gov. If you accept these terms and conditions, you will need to complete the following fields in the application:

Sponsor Information:

- Registering IND/IDE trials? (*Select “yes” or “no”*)
- Type of Organization – University
- Organization Name – “University of Illinois at Chicago, University of Illinois Medical Center at Chicago”
- Organization Address – 1737 West Polk Street, Chicago, IL, 60612
- Organization Abbreviations and Acronyms – UIC; UIMC
- Parent Organization, if any – None
- Official Representative – Jennifer Rowan
- Phone – (312) 413-2326
- Email – jrowan@uic.edu
- Organizational URL – www.uic.edu
- Funding Organization – (*List funding source if applicable*)

Investigator Information:

- Investigator Name – (*List principal investigator’s name*)
- Affiliation (if not the sponsor) – (*Do not list anything in this field if the investigator is affiliated with UIC, which is the sponsor*)
- Investigator Phone – (*List principal investigator’s phone number*)
- Investigator Email – (*List principal investigator’s email address*)

Regulatory Information:

- Regulatory Authority – (*List United States Food and Drug Administration as the Regulatory authority if the research involves an investigational drug, device or biologic. Otherwise, list University of Illinois at Chicago Institutional Review Board as the regulatory authority.*)
- Regulatory Authority Address – (*If FDA is listed as the regulatory authority, use the following address: 5600 Fishers Lane, Rockville, MD 20857. If the UIC IRB is listed as the regulatory authority, use the following address: Office for the Protection of Research Subjects (OPRS), M/C 672, 1737 West Polk Street, Chicago, IL, 60612.*)
- When finished, select “Submit Application” at the bottom of the application page.
- Within approximately 1- 2 days you will receive an email from ClinicalTrials.gov Registration that gives you a user name and password and

instructs you to login and change your password as soon as possible. The email will also provide the PRS web site address for the registration process.

Instructions to Register a Clinical Trial

- To register a clinical trial, login to the PRS web site for the registration process. This will take you to the Main Menu page that provides you with several options, including “Change password” under “User Account”.
- Under “Help” you will receive detailed instructions by selecting “User’s Guide” or definitions of the different fields by selecting “Data Element Definitions”.
- To register a trial, select “Create” under “Protocol Records”.
- One section of the registration form asks for information regarding human subjects review. The following are suggested entries for these fields.
 - For Board Approval Number – *(List the IRB Protocol number assigned to your research)*
 - For Board Name – University of Illinois at Chicago IRBs #1, #2, #3, or #4
 - For Board Affiliation – University of Illinois at Chicago
 - For Board Chair:

IRB #1

Name: [Albert](mailto:albert@uic.edu)

Phone: 312-996-1711

Email: albert@uic.edu

IRB #2

Name: Susan Labott, PhD

Phone: 312-996-1711

Email: labott@uic.edu

IRB #3

Name: Paul Heckerling, MD

Phone: 312-996-1711

Email: pshecker@uic.edu

IRB#4

Name: Kathryn Rugen, PhD, RN

Phone: 312-996-1711

Email: kathryn.rugen@med.va.gov

Address

Office for the Protection of Research Subjects, M/C 672

1737 West Polk Street

Chicago, IL, 60612, USA

- Oversight Authorities – *(List United States Food and Drug Administration as the oversight authority if the research involves an investigational drug, device or*

biologic. Otherwise, list United States: Institutional Review Board as the oversight authority.)

- Please use “University of Illinois at Chicago” when asked for your affiliation or facility.

The complete list of data elements required by the FDAAA and their definitions is available at the ClinicalTrials.gov sites, available at - <http://prsinfo.clinicaltrials.gov/definitions.html>.

Additional Information:

For further information and guidance about which clinical trials should be registered, who is responsible for registering the trial, the registration process, or the results reporting requirements refer to:

- PRS and U.S. Public Law Page available at <http://prsinfo.clinicaltrials.gov/fdaaa.html>
- “Is This Clinical Trial Fully Registered?: A Statement from the International Committee of Medical Journal Editors,” available at <http://www.icmje.org/~ijae/ { æ € } .htm>
- Guidance from NIH Office of Extramural Research “Clinical Trials Registration in ClinicalTrials.gov (Public Law 110-85): Competing Applications and Non-Competing Progress Reports” - , Title VII,” available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-023.html>
- Guidance from NIH Office of Extramural Research “Reporting ‘Basic Results’ in ClinicalTrials.gov.” *Chest* 2009; 136:295-303.

REVISION LOG:

Version (#, date)	Replaces (#, date)	Summary of changes
2.1, 10/07/2008	2.0, 12/21/2007	Clarification of regarding the registration of pediatric postmarket surveillance of devices; Update of weblinks; Addition of IRB #4 information, Addition of information regarding Basic Results (draft) link.
2.2, 1/05/09	2.1, 10/07/08	Insertion of “Additional Information” section and new link
2.3, 4/20/10	2.2, 1/05/09	Insertion of additional information and links related to basic results reporting, addition of IRB#2 chair information.