CONTRACT AND GRANT OFFICERS

Subject: Registration of Clinical Trials – new Federal legislation and expanded ICMJE requirements

Background

In its implementation of the Drug Modernization Act (FDAMA) of 1997, the federal Food and Drug Administration (FDA) mandated that all clinical trials testing FDA-regulated drugs for efficacy in serious or life-threatening diseases or conditions must be registered on a publicly-available database. As a result, the website known as ClinicalTrials.gov, established and maintained by the National Institutes of Health (NIH), was created.

In 2005, the International Committee of Medical Journal Editors (ICMJE) began requiring registration of clinical trials that began subject recruitment on or after July 1, 2005 in public registries as a prerequisite for publication with a stated goal of promoting public good by making the existence and design of such trials publicly available. They defined a clinical trial as “Any research project 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.” An ‘intervention’ includes “drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.” The policy specifically excluded registration requirements for FDA Phase I trials whose “primary goal is to assess major unknown toxicity or determine pharmacokinetics.” The eleven members of the ICMJE adopted this policy which required registration on one of a number of recommended public databases, including ClinicalTrials.gov. Many other non-member journals, including non-medical journals, have adopted ICMJE requirements, and the ICMJE maintains a list of journals that claim to adhere to its requirements.

New revisions to the FDAMA:

1) What trials to register?

In September 2007, the FDAMA was amended to expand the registration requirement for all “applicable clinical trials,” including Federal, industry-sponsored and investigator-initiated trials that are:

“1) Trials of Drugs or Biologics which are controlled clinical investigations, other than Phase I trials, of a product subject to FDA regulation and;

2) Trials of Devices which are controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarketing studies.”
Additionally, the amended Act expands the scope of registration information that was previously optional, such as information regarding trial results or outcomes.

The FDAMA amendment also provides significant penalties for failing to register or for providing false or misleading information in connection with applicable trials and may include civil monetary penalties and, for trials that are federally funded, withholding or recovery of grant funds.

2) When to Register?

Trials initiated after September 27, 2007 or trials that are ongoing as of September 26, 2007 that do involve a “serious or life-threatening disease or condition” must be registered in full by the later of September 26, 2007 or 21 days after the first subject is enrolled.

Trials that were ongoing as of September 27, 2007 that do not involve a “serious or life-threatening disease or condition” must be registered by September 27, 2008.

Trials that were ongoing as of September 27, 2007 that do involve a “serious or life-threatening disease or condition” and were completed by September 26, 2007 are not subject to this requirement, though may be subject to pre-existing registration requirements.

3) Who Must Register?

The “responsible party” who must register the trial is defined by statute as either:

- the sponsor of the clinical trial as defined in 21 CFR 50.3; i.e. the holder of an IND or IDE
- the principal investigator if s/he is so designated by the sponsor

4) Application and Progress Report Requirements for NIH-Funded Grants

Competing (new and renewal) applications submitted on or after 1/15/08 and non-competing progress reports with budget start dates on or after 4/1/08 that include clinical trials must be registered with ClinicalTrials.gov and include basic trial registration data. If a new applicable trial is proposed in a competing application, the research plan should include a statement that the application includes a trial that requires registration in ClinicalTrials.gov.

Expanded requirements by ICMJE:

Also in 2007, the ICMJE expanded the scope of trials to be publicly registered to include “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects of health outcomes.” Specifically, this now includes Phase I clinical trials.

Presently, the ICMJE follows the 2005 guidelines and does not enforce the inclusion of Phase I trials, however, trials where enrollment begins on or after July 1, 2008 will need to comply with the ICMJE’s 2007 requirements in order to have publications accepted by member journals.
Summary

While the FDAMA requirements are narrower than what will soon be required by the ICMJE, particularly concerning the issue of Phase I trials, the ICMJE encourages researchers to err on the side of more broad registration to ensure manuscripts will meet standards of acceptability. Additional information can be found on the ICMJE’s Frequently Asked Questions document located at: http://www.icmje.org/faq.pdf.

With respect to the expanded scope of information that the FDAMA will eventually require be listed on ClinicalTrials.gov, such as trial results, we hope to have an opportunity to submit comments as part of any rulemaking process by the FDA, and in advance of expansion of data fields on the website. Once the FDA issues further guidance, RAO will issue additional guidance to campuses.

Please refer to the following links for additional guidance and FAQs:


Refer: Dianne Archer
(510) 987-0355
Dianne.Archer@ucop.edu

Dianne Archer, J.D.
Coordinator-Private Contracts & Grants
Notice Number: NOT-OD-08-014 -- (See Additional information in NOT-OD-08-023.)

Key Dates
Release Date: November 16, 2007

Issued by
National Institutes of Health (NIH), (http://www.nih.gov)

A new law has been enacted to expand the scope of ClinicalTrials.gov. This notice provides information for NIH grantees on new responsibilities related to the first part of the law, the registration of clinical trials.

New Law Enacted to Expand ClinicalTrials.gov:

Public Law 110-85, which was enacted on September 27, 2007 [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf] amends the Public Health Service Act to expand the scope of clinical trials that must be registered in ClinicalTrials.gov. It also increases the number of registration fields that must be submitted, requires certain results information to be included and sets penalties for noncompliance. This notice provides information for NIH grantees and contractors on new responsibilities related to the first part of the law, the registration of clinical trials. Additional information will be forthcoming.

Which Trials Must be Registered?

The trials that must be registered are called “applicable clinical trials.” Under the statute, these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. You should review the statutory definition of applicable clinical trial to identify if any of your trials must be registered to comply with the law [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf] See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). NIH encourages registration of ALL trials whether required under the law or not.

Who is responsible?
The entity responsible for registering is the “responsible party.” The statute defines the responsible party as:

1) the sponsor of the clinical trial (as defined in 21 C.F.R. 50.3) [http://a257.q.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqr/pdf/21cfr50.3.pdf], or

2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (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.) [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf] See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(I)).

How do you determine if you are a responsible party?

Investigators are encouraged to consult with their sponsored research office, institutional counsel, or other partners to determine if they are the “responsible party” for registering a trial. It is your responsibility to determine if you are obligated to register any of your clinical trials.

1) If you are the Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) holder, you may be the “sponsor” as that term is defined in the FDA regulations found at 21 C.F.R. 50.3. For studies that are conducted under an IND or IDE, the “sponsor” is identified in the course of filing the IND (commonly called the “IND holder” or the “part 812 sponsor”) OR

2) You may not be the sponsor, but if you are the Principal Investigator you may have been delegated registration duties by the sponsor.


3/24/2008
3) For extramural trials, where there is no IND or IDE holder, NIH would not be the responsible party. The funding recipient may be a "responsible party" as that term is defined in the Act, depending on the unique circumstances of the trial.

**When Must I Register My Trial?**

1) Trials initiated after 9/27/2007, or trials that are ongoing as of 12/28/2007 must be registered in full by: The later of 12/26/2007 or 21 days after the first patient is enrolled.

2) Trials that were "ongoing" as of as of 9/27/2007 and do not involve a "serious or life threatening disease or condition," must be registered by 9/27/2008.

3) Trials that were "ongoing" as of as of 9/27/2007, do involve a "serious or life threatening disease or condition," and are completed (meaning, not "ongoing") by 12/26/2007 are not subject to these requirements, though they may be subject to pre-existing registering requirements.

("Ongoing" in this context means a trial had one or more patients enrolled, but had 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.)

**What are the penalties for failing to register an “applicable clinical trial?”**

Penalties for responsible parties who fail to register, or provide false or misleading information in connection with, applicable clinical trials are significant and may include civil monetary penalties and, for federally-funded trials, the withholding or recovery of grant funds. See PL 110-85, Sections 801(a), (b), (adding new 42 U.S.C. 282(j), and new 21 U.S.C. 331(j)).

**Obtaining Assistance from NIH:**

Existing mechanisms established by NIH ICs to assist funding recipients in registering trials with ClinicalTrials.gov can continue to be used to assist responsible parties with the new registration requirements. A list of IC liaisons is provided below. While the NIH anticipates the continuation of this service, it is important to remember that the IC cannot in any way substitute for the responsible party in fulfilling its statutory duties. When requesting registration assistance from an IC, you are responsible for ensuring that all necessary information is provided to the IC in sufficient time to review and coordinate before the statutory deadlines described above for submission to ClinicalTrials.gov are triggered. You will need to stay in contact with the IC liaison to ensure that your information has been registered properly. Submission of registration information to an IC is not sufficient to satisfy the statutory obligations for submission to ClinicalTrials.gov. Alternatively, you may register your trial directly by following the procedures outlined at [http://prsinfo.clinicaltrials.gov/](http://prsinfo.clinicaltrials.gov/).

Additional information on the new registration requirements is available on the PRS Web site [http://prsinfo.clinicaltrials.gov/](http://prsinfo.clinicaltrials.gov/).

---

**Weekly TOC for this Announcement**

NIH Funding Opportunities and Notices

---

**Office of Extramural Research (OER)**

**National Institutes of Health (NIH)**

9000 Rockville Pike

Bethesda, Maryland 20892

**Department of Health and Human Services (HHS)**

---

**Note:** For help accessing PDF, RTF, MS Word, Excel, PowerPoint or RealPlayer files, see Help Downloading Files.


3/24/2008
NOT-OD-08-023: Clinical Trials Registration in ClinicalTrials.gov (Public Law 110-85): Competing Ap...

Clinical Trials Registration in ClinicalTrials.gov (Public Law 110-85): Competing Applications and Non-Competing Progress Reports

Notice Number: NOT-OD-08-023

Key Dates
Release Date: December 21, 2007

Issued by
National Institutes of Health (NIH), (http://www.nih.gov)

Recent legislation has expanded the scope of ClinicalTrials.gov (see NOT-OD-08-014). This notice provides information to NIH applicants and grantees on new responsibilities related to registration of their “applicable clinical trials” in ClinicalTrials.gov.

New Law Enacted to Expand ClinicalTrials.gov:

Public Law 110-85 (also known as the FDA Amendments Act), which was enacted on September 27, 2007 [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf] amends the Public Health Service Act to mandate registration and results reporting of “applicable clinical trials” (see below) in ClinicalTrials.gov. This legislation also includes a requirement that if an “applicable clinical trial” is funded in whole or in part by a grant from any agency of the Department of Health and Human Services, any grant or progress report shall include a certification that the responsible party has made all required submissions for the applicable trial to ClinicalTrials.gov.

Which Trials Must be Registered and Certified in Grant Applications and Progress Reports?

Under the statute, the “applicable clinical trials” trials generally include:

1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation;

2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance.

How To Determine If This Applies To Your Research?

The entity responsible for registering is the “responsible party.” The statute defines the responsible party as:

1) the sponsor of the clinical trial (as defined in 21 C.F.R. 50.3) [http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqtr/pdf/21cfr50.3.pdf], or

2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (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.) [http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf] See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

Investigators are encouraged to consult with their sponsored research office, institutional counsel, or other institution officials to determine if they are the responsible party for registering a trial. It is the applicant or grantee’s responsibility to determine if they are obligated to register their clinical trials under this legislation. For NIH-funded clinical trials where there is an IND holder, consistent with FDA regulations, the IND holder is the sponsor, and will be considered the responsible party unless this obligation is delegated to the principal investigator. For NIH-funded clinical trials where there is no IND holder, the funding recipient will be considered the responsible party.

When Must I Register My Trial?

1) Trials initiated after 9/27/2007, or trials initiated before that date and ongoing on 12/26/2007 that involve a “serious or life threatening disease or condition,” must be registered in full by: the later of 12/26/2007 or 21 days after the first patient is enrolled.
2) Trials that were initiated before 9/27/07 that are "ongoing" as of 12/26/2007, and which do not involve a "serious or life threatening disease or condition," must be registered by 9/27/2008.

3) Trials that were initiated before 9/27/07 and are "ongoing" as of 12/26/2007, which do involve a "serious or life threatening disease or condition," and are completed (meaning, not "ongoing") by 12/26/2007 are not subject to these requirements, though they may be subject to pre-existing registering requirements. ("Ongoing" in this context means a trial had one or more patients enrolled, but had not reached its "completion date," meaning, 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.)

How are Trials Registered?

To register go to the ClinicalTrials.gov Protocol Registration System Information Website (http://prsinfo.clinicaltrials.gov/) and follow directions for registration of any and all "applicable clinical trials" included in the competing application or active grant. A unique identifier, called an "NCT" number, will be generated during the registration process.

What Needs To Be Included in Grant Applications and Progress Reports To Provide Certification?

For competing applications (new and renewal) that include applicable clinical trial(s): the NCT number/s, Brief Title/s (as defined by ClinicalTrials.gov, see http://prsinfo.clinicaltrials.gov/s801-new-requirements.pdf), and the identity of the responsible party (or parties) must be provided in the Human Subjects Section of the Research Plan. If a new applicable clinical trial is proposed, the human subjects section of the research plan should include a statement that the application includes a trial which requires registration in ClinicalTrials.gov. The signature on the application of the Authorized Organizational Representative will now also assure compliance for the registration of any such trial.

When submitting a non-competing progress report that includes applicable trial(s): NCT number/s, Brief Title/s (as defined by ClinicalTrials.gov, see http://prsinfo.clinicaltrials.gov/s801-new-requirements.pdf), and the identity of the responsible party (or parties) are to be included in the Human Subjects section of the progress report.

When Does The Requirement to Report Trial Registration Go Into Effect?

Competing applications: All applications submitted to the NIH on or after January 25, 2008, which incorporate an applicable clinical trial in their proposed project, are required to provide the information as detailed above.

Non-competing progress reports: All progress reports for grants which include an applicable clinical trial with budget start dates of April 1, 2008 or later are required to provide the information as detailed above.

What Are The Penalties For Failing To Register An "Applicable Clinical Trial"?

Penalties for responsible parties who fail to register, or provide the assurance described above to the NIH, or who submit false or misleading information in connection with "applicable clinical trials" are significant, and may include civil monetary penalties and, for federally-funded trials, the withholding or recovery of grant funds. See PL 110-85, Sections 801(a), (b), (adding new 42 U.S.C. 282(j), and new 21 U.S.C. 331(j)). NIH will verify that each "applicable clinical trial" for which the grantee is the responsible party has been registered in ClinicalTrials.gov.

Obtaining Assistance From NIH:

You may register your trial directly by following the procedures outlined at http://prsinfo.clinicaltrials.gov/.

Alternatively, you may request registration assistance from an NIH Institute or Center (IC), in which case you are responsible for ensuring that all necessary information is provided to the IC in sufficient time to review and coordinate before the statutory deadlines described above for submission to ClinicalTrials.gov are triggered. You will need to stay in contact with the IC liaison to ensure that your information has been registered properly. Submission of registration information to an IC is not sufficient to satisfy the statutory obligations for submission to ClinicalTrials.gov. You remain legally responsible for submission of information to ClinicalTrials.gov in accord with all applicable legal mandates.

For additional information please see FAQ: http://grants.nih.gov/grants/policy/hs/faqs_aps_clinical_trials.htm
Inquiries regarding this Notice should be directed to:

Office of Extramural Programs
Office of Extramural Research
National Institutes of Health
Email: OEPMailbox@mail.nih.gov

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint or RealPlayer files, see Help Downloading Files.