University of Wisconsin-Madison Guidance for Registration of Studies at ClinicalTrials.gov

Approved by Clinical Trials Registration Committee
June 24, 2006

History

Over the last ten years, the federal government and the International Committee of Medical Journal Editors (“ICMJE”) have issued various laws and directives, respectively, on the subject of clinical trial registration. The registration effort began with the development of the ClinicalTrials.gov website, which is publicly available. It is a service of the National Institutes of Health, developed by the National Library of Congress.

In 1997, the FDA began requiring registration of a limited number of trials. The Food and Drug Administration Amendments Act of 2007 (“FDAAA”) expanded the scope of trials that must be registered.

In 2004, the ICMJE issued a directive regarding which trials must be registered in order to be considered for publication in journals that adhere to ICMJE standards. In 2007, the ICMJE also expanded the definition of trials that must be registered.

FDA Requirements for Registration

The FDAAA requires registration of all “applicable clinical trials” (whether federally or privately funded). These include:

- Applicable drug and biologic trials: Controlled clinical investigations, other than Phase I investigations, of a drug or biologic subject to the Food, Drug & Cosmetic Act (“FDCA”).
- Applicable device trials:
  - Prospective clinical studies of health outcomes comparing an intervention with a device subject to the FDCA against a control in human subjects (other than a small clinical trial 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); and
  - Pediatric postmarket surveillance studies, as required under the FDCA.

In summary, those studies that must be registered include all phase 2-4 interventional (e.g. subjects are assigned to one or more arms) drug, biologic or device trials. This is true regardless of whether or not the trial is used to support a new FDA application.
ICMJE Requirements for Registration

The ICMJE requires the following studies to be registered: “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.” This definition includes Phase I trials.

According to ICMJE, 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. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.”

Differences between FDA and ICMJE Requirements

One of the biggest differences between the FDA requirements and the ICMJE requirements is that the FDA does not require registration of Phase I trials, while ICMJE does require registration of Phase I trials.

The FDA requires registration of only controlled drug, biologic and device studies (with the exception of postmarketing pediatric studies of devices), while the ICMJE requires registration of controlled and uncontrolled drug, biologic and devices studies, as well as, non-drug, biologic and device studies such as dietary interventions and behavioral treatments.

Responsibility to Register

- Investigator-initiated studies: registration is the responsibility of the PI*;
- NIH-sponsored trials: registration should be completed by the grantee of the funds;
- Industry-sponsored trials: registration should be completed by the trial sponsor;
- Trials involving an IND or IDE: registration should be completed by the holder of the IND or IDE (PI*’s who hold their own IND or IDE are responsible for registration);
- Trials in which the sponsor has declined to register: registration may be the responsibility of the PI*. Please contact UW Research & Sponsored Programs or Office of Administrative Legal Services for more assistance.

*If the PI is responsible for registration, the PI may designate an individual to register his/her protocols and complete registration information, however, it is ultimately the responsibility of the PI to assure registration occurs and the accuracy of the information entered.
FDA Timeframe for Registration

The FDAAA requires that all trials be registered as follows:

- Trials initiated after 9/27/2007, or trials that are ongoing as of 12/26/2007, must be registered by the later of 12/26/2007 or 21 days after the first patient is enrolled;
- Trials that are 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.

The term “ongoing” means that one or more patients is enrolled in the clinical trial and the final subject has not yet been examined or received an intervention for the purposes of final collection of data for the primary outcome.

ICMJE Timeframe for Registration

Trials that began before July 1, 2005:
Investigators should register trials that began enrolling patients any time before July 1, 2005 as soon as possible if they wish to submit them to a journal that follows the ICMJE policy. However, beginning on September 13, 2005, ICMJE journals will consider such trials only if they were adequately registered before journal submission. The ICMJE journals will accept "retrospective registration" of trials that began before July 1, 2005 (retrospective meaning registration occurs after patient enrollment begins).

Trials that began after July 1, 2005:
ICMJE journals will consider trials beginning on or after July 1, 2005 only if registration occurred before the first patient was enrolled (“prospective registration”).

Penalties for Failure to Register

Penalties for failing to register applicable clinical trials, or for providing false or misleading information in connection with, are significant and may include civil monetary penalties and, for federally-funded trials, the withholding or recovery of grant funds. Civil monetary penalties include a $10,000 fine per violation. After notification of noncompliance, the fine may go up to $10,000 per day until resolved.

Unregistered trial will not be considered for publication in journals that adhere to ICMJE standards.

How to Register

The University of Wisconsin is already registered as an institution at ClinicalTrials.gov and has appointed ClinicalTrials.gov administrators to assist UW investigators or their designees in
establishing their Protocol Registration System accounts. Investigators or their designees should contact the appropriate UW ClinicalTrials.gov administrator listed below for assistance with protocol registration requirements and other guidance information. The ClinicalTrials.gov administrators are also responsible for releasing information that has been entered by the investigator into the ClinicalTrials.gov system and for following up on ClinicalTrials.gov inquiries.

- For all cancer-related protocols, contact:
  Shari Zeldin, Comprehensive Cancer Center
  @ (608) 263-8403 or swzeldin@uwcarbone.wisc.edu

- For all other protocols, contact:
  Tina Graber, Office of Clinical Trials
  @ (608) 265-6506 or tmg@clinicaltrials.wisc.edu

**Stepwise instructions for ClinicalTrial.gov trial registration is as follows:**

1. To request a user log on name and temporary password, send an email message to your assigned UW ClinicalTrials.gov administrator:
   - swzeldin@uwcarbone.wisc.edu (all cancer-related protocols)
   - tmg@clinicaltrials.wisc.edu (all other protocols)

2. Include in the message your name, telephone number, and email address.

3. You will receive a reply to your email with a login name and a temporary password which will allow you to register your protocol(s).

4. Go to the ClinicalTrials.gov registration website at https://register.clinicaltrials.gov/

5. Complete the login fields. In the “Organization” field, state “UWisconsin”

6. On the Main Menu page, under “User Account,” follow the instructions to change your temporary password as soon as possible. Refer to the “User’s Guide” for additional information. The “User” is responsible for entering the information about the trial, ensuring that the information is correct, and updating the information in a timely manner.

7. On the Main Menu page, under Protocol Record, hit "Create" and complete the study description template. Note that the ClinicalTrials.gov-required fields are marked with a red asterisk (*) and the FDA-required fields are marked with a green FDAAA. Taken together, these data elements represent the requirements for an adequate registration. If you do not complete these fields, your trial may not be considered "fully registered." Note also that each field of the template is labeled and linked to a definition; however, several fields are potentially confusing and should be completed as follows:

   - Organization’s Unique Protocol ID: Use the UW IRB number.
• Sponsor: Enter “University of Wisconsin” (even though the UW may not be the actual trial sponsor.
• Collaborators: Sponsorship can be clarified by entering the actual sponsor’s name. For unsponsored research, either leave the field blank or enter "None".
• Record Verification Date: Enter the date on which you complete and submit the template.
• Conditions: Use the MeSH controlled vocabulary (link provided in the conditions field). If you don’t, ClinicalTrials.gov staff is likely to delete your term and choose one of their own.
• Keywords: Use the MeSH controlled vocabulary (link provided in the keywords field). If you don’t, ClinicalTrials.gov staff is likely to delete your term and choose one of their own.

8. If the User is not the PI, the User must ensure the PI has reviewed and approved the information before submitting.

9. Submit the completed, PI-approved, template (note: you will receive a warning message if required fields are incomplete; complete the missing information and submit). The completed template will go to the UW administrators listed above. The appropriate administrator will check to be sure that the trial has been approved by the IRB and will release the template to ClinicalTrials.gov

10. The PI or designee is responsible for periodic updates to the study record, e.g., for study-specific changes such as recruitment status and protocol revisions (see below for more instructions). The PI or designee is also responsible for verifying the study record once every 12 months.

Making Periodic Updates to Registration

Please note that anytime you access your trial information to perform updates or review information, MAKE SURE TO update the “Record Verification Date” field.

• Recruitment status changes:
  If recruitment status changes you must submit an update noting such within 30 days of the change in recruitment status

• Completion of trial:
  If the clinical trial has completed, you must submit an update noting such within 30 days of the completion of the trial

• Other changes:
  If any of the information you submitted has changed, you must submit an update of those changes at least once every 12 months (see above bullets for deadlines associated with changes in recruitment or trial completion). The update must include the dates of any such changes.
• If no changes:
  If no changes have been made in the proceeding 12 months, you still must go in to the record and update the “Record Verification Date” field and resubmit the protocol for release by the clinicaltrials.gov administrator.

### Reporting Results of the Study

If you are the person responsible for registering a trial, you must also submit information on basic results.

Such information must include for each applicable clinical trial for an approved drug or for a cleared or approved device the following elements:

- Demographic and baseline characteristics of the patient sample, including the number of patients who dropped out of the trial and the number of patients excluded from the analysis;
- Primary and secondary outcomes, including the results of scientifically appropriate tests of the statistical significance of such outcome measures;
- Point of contact for scientific information about the trial results; and
- Whether there exists an agreement between the sponsor and the PI that restricts in any manner the ability of the PI, after completion of the trial, to discuss or publish the results of the trial.

The information described above generally must be submitted not later than 1 year after the earlier of:

- The estimated completion date of the trial (that projected at the outset of the study); OR
- The actual date of completion.

### Reporting Adverse Events that Occurred in the Study

Effective September 27, 2009, adverse events must be part of results reporting and include:

- A table of anticipated and unanticipated serious adverse grouped by organ system, with number and frequency of such event in each arm of the clinical trial; and
- A table of anticipated and unanticipated adverse events not included in the table described above that exceed a frequency of 5% within any arm of the clinical trial, grouped by organ system, with number and frequency of such event in each arm of the clinical trial.

For more information, go to: [http://prsinfo.clinicaltrials.gov](http://prsinfo.clinicaltrials.gov) and scroll down to the bottom of the page to the link entitled: “Basic Results” Data Element Definitions.
More information

FDA Information Page:
http://www.fda.gov/oashi/clinicaltrials/section113/

FDA Amendments Act of 2007:

ICMJE Clinical Trial Registration FAQ’s:
http://www.icmje.org/faq.pdf

NIH Guidance on New Results Database:

Contacts

To register a study at ClinicalTrials.gov, contact:

- For all cancer-related protocols, contact:
  Shari Zeldin, Comprehensive Cancer Center
  @ (608) 263-8403 or swzeldin@uwcarbone.wisc.edu

- For all other protocols, contact:
  Tina Graber, Office of Clinical Trials
  @ (608) 265-6506 or tmg@clinicaltrials.wisc.edu

For other questions concerning this guidance, contact:

Jim Wells, Office of Research Policy
@ (608) 262-0558 or jawells2@bascom.wisc.edu