

REGISTERING STUDIES AT CLINICALTRIALS.GOV - FAQs ABOUT THE FDA/NIH/ICMJE REQUIREMENTS

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What is the requirement?

Over the past ten years, government agencies and the International Committee of Medical Journal Editors have issued laws and directives on the subject of trial registration. All parties have consistently agreed that the purpose of trial registration is to promote the

public good by ensuring that the existence and design of clinically directive trials are publicly available. The registration effort began with the development of a publicly available Web site, ClinicalTrials.gov. ClinicalTrials.gov is a service of the NIH, developed by the National Library of Congress.

In 1997, the FDA/NIH began requiring registration for only a limited number of trials, Then, in September, 2007, the Food and Drug Amendments Act (Title VIII. Sec. 801) significantly expanded the scope of clinical trials that must be registered. Penalties for failing to register “applicable trials” may include civil monetary penalties.

In 2004, the International Committee of Medical Journal Editors (ICMJE) defined trials that must be registered in order to be considered for publication in journals that adhere to ICMJE standards. In 2007 the ICMJE expanded the definition of trials that must be registered. Scores of journals (not limited to medical journals) have adopted the registration policy.

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For registration purposes, how is “clinical trial” defined and what are the registration deadlines?

According to the International Committee of Medical Journal Editors (ICMJE):

2005 definition statement: “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. The trial must have at least one prospectively assigned concurrent control or comparison group in order to trigger the requirement for registration.” *This definition specifically excluded Phase I trials.*

2007 definition statement: “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.*

Deadlines for registration: Currently, the ICMJE follows its 2005 definition. The ICMJE will start to implement the expanded (2007) definition for all trials that begin enrollment on or after July 1, 2008. The ICMJE will not strictly impose this expanded definition until the stated date. *However, trials that meet the expanded definition CAN be registered before the stated date, and the ICMJE encourages investigators to do so, noting that such action is consistent with their goal of “full transparency with respect to performance and reporting of clinical trials.*

According to the FDA and the NIH:

1997 Definition: The Food and Drug Modernization Act, later clarified by FDA guidance documents, required sponsors to register clinical trials conducted under an investigational new drug application (IND) for drugs or biological agents intended to treat a serious or life-threatening disease or condition and intended to test effectiveness.

2007 Definition: The Food and Drug Amendments Act (Title VIII. Sec. 801) requires registration for all “applicable clinical trials,” including Federal, industry-sponsored, and investigator-initiated that are:

- 1) Trials of drugs and biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation, and
- 2) Trials of devices: Prospective clinical studies of health outcomes comparing an intervention with a device against a control in human subjects (other than small clinical trials to determine the feasibility of a device, or clinical trials 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 Federal Food, Drug and Cosmetic Act.

Deadlines for registration: This Food and Drug Amendments Act of 2007 requires that all trials, regardless of sponsor, initiated after 9/27/07 or ongoing as of 12/26/07 must be registered in full by the later of 12/26/07 or 21 days after the first patient is enrolled. All

trials that were ongoing as of 9/27/07 and do not involve serious or life-threatening conditions must be registered by 9/27/08.

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What are the penalties for failing to register?

According to the ICMJE:

Unregistered trials will not be considered for publication in journals that adhere to ICMJE standards. This penalty has not changed over time.

According to the FDA/NIH (Food and Drug Amendments Act of 2007):

Penalties may include civil monetary penalties up to \$10,000 fine for failing to submit or for submitting fraudulent information to ClinicalTrials.gov. After notification of noncompliance, the fine may go up to \$10,000 per day until resolved. For federally funded grants, penalties may include the withholding or recovery of grant funds.

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Who is responsible for registering a trial?

Normally, the clinical trial will be registered by the sponsor.

- NIH-sponsored trials should normally be registered by the Institute that is funding the research
- Industry-sponsored trials (industry-written protocol) should normally be registered by the industry sponsor.
- Multi-site trials should be coordinated among the sites and registered by the “lead sponsor” so that ClinicalTrials.gov does not receive multiple registrations for the same trial.

However, some trials will need to be registered by the PI.

- Investigator-initiated trials (for which industry has supplied drug or grant funds) should normally be registered by the PI.
- Trials for which PIs hold their own INDs or IDEs should normally be registered by the PI. (PIs who hold their own INDs or IDEs are considered to be the trial sponsors.)
- Trials that the sponsor has declined to register.

The PI is ultimately responsible for determining that registration requirements are met. Although some sponsors will do the actual registration work, it is still the PI's responsibility to ensure that the registration has been accomplished. Before enrolling subjects, every PI should ask the study's sponsor, "Is this study fully registered?" If the sponsor responds affirmatively, PIs should personally check ClinicalTrials.gov to ensure that the trial has been registered.

For registration instructions at the KUMC, see below "How do PIs register their trials?"

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The terms "health-related interventions" and "health outcomes" suggest that this requirement applies only to biomedical clinical trials. Is that correct?

No. According to the 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.

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Are there any exceptions?

Yes. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration.

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What if I am uncertain about whether to register my trial?

According to the ICMJE:

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

According to the FDA and the NIH:

Both agencies encourage the registration of ALL trials, whether or not required under the FDA Amendments Act of 2007.

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Where / what are the registries?

Over time, ClinicalTrials.gov has become the registry of choice and is now the registry required by the FDA Amendments Act of 2007. ClinicalTrials.gov is a service of the NIH, developed by the National Library of Medicine.

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How is the KUMC involved?

KUMC is already registered as an institution at ClinicalTrials.gov, and hundreds of KUMC-based trials have already been registered at this site. In addition, ClinicalTrials.gov asks each institution to identify a PRS administrator. At KUMC, the administrator is Diana Naser RN, Division Director, Clinical Research Administration in the Research Institute.

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Is existing KUMC practice affected by the new FDA/NIH registration requirement?

From the beginning, the KUMC has promoted registration of trials/studies meeting the broad ICMJE definition. Therefore, the new FDA law does not expand the scope that KUMC has applied for registering studies in the past, nor does the new FDA law change the KUMC existing practice for defining the “responsible party” for registering a trial.

What *has* been affected by the new FDA law is the penalty for noncompliance. As explained above at “What are the penalties for failing to register?” and in the information references below, failing to register applicable trials on ClinicalTrials.gov may now include civil monetary penalties and, for federally funded trials, the withholding or the recovery of grant funds. The ICMJE penalty for failure to register continues to be the journals’ refusal to consider publication of trial results.

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How do PIs register their trials?

If after reading this information, you determine that you need to register your clinical trial at ClinicalTrials.gov, call your trial's sponsor/program officer. Ask whether the trial has already been registered and/or whether the sponsor intends to register the trial.

- If the answer is "no" to both questions, proceed to step 1., below.
- If the sponsor states that the trial has already been registered, check the information about your trial on ClinicalTrials.gov., e.g., for multi-site studies, be sure that your site is listed and that the information is accurate.
- If the sponsor intends to register the trial, be sure that registration occurs before you enroll your first subject. Once the trial has been registered, check the record for accuracy.

To register your trial:

Documents, forms and instructions to assist with the registration process can be found at

the Research Institute website

(http://www2.kumc.edu/researchinstitute/cra/new_clinical_trial_reg_require.html.)

In addition, the Research Institute can submit clinical trials to ClinicalTrials.gov on behalf of an investigator. Completed clinical trials registration forms, along with a copy of the HSC approval letter, should be submitted to Diana Naser RN (dnaser@kumc.edu) in the Clinical Research Administration division. Please feel free to contact Diana Naser at (913) 588-1242 should you require assistance or have any questions.

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Does the registration posting need review by the Human Subjects Division?

No. The KUMC/RI Administrator will check with the Human Subjects Division to ensure that studies posted on ClinicalTrials.gov have been approved, but the KUMC Human Subjects Division will not review the postings.

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Is more information available?

Yes.

For more information about the ICMJE registration requirement, see:

The 2007 ICMJE editorial entitled “[Clinical Trials Registration: Looking Back and Moving Ahead.](#)”

For more information about the FDA Amendments Act of 2007, see:

Guidance from the [NIH Office of Extramural Research](#)

[NIH Fact Sheet](#)

[AAMC memorandum](#)

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