

Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Publishing and Editorial Issues Related to Publication in Biomedical Journals: Obligation to Register Clinical Trials

University of Louisville researchers are strongly encouraged to register any research that appears to meet the [FDAAA](#) definitions at ClinicalTrials.gov or ICMJE definitions below. If there is any question at all about whether or not a study should be registered, then it should probably be registered. Registering after the work has been completed is not acceptable. The consequence of not registering, if a journal editor thinks the study should have been registered, is refusal by a journal to publish the work.

It is important to note that the FDAAA requirement for a “responsible party” to register “applicable clinical trials” is more narrow than the ICMJE requirement to register clinical trials. “Applicable clinical trials” generally include interventional studies (with one or more arms) of drugs, biological products, or devices that are subject to FDA regulation, meaning that the trial has one or more sites in the U.S, involves a drug, biologic, or device that is manufactured in the US (or its territories), or is conducted under an investigational new drug application (IND) or investigational device exemption (IDE). For the complete statutory definitions and more detailed information on the agency's current thinking about their meaning, see this [pdf document](#).

The ICMJE believes that it is important to foster a comprehensive, publicly available database of clinical trials. The ICMJE’s expanded definition of a clinical trial is any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.

The ICMJE participating journals and organizations and their representatives who approved the revised Uniform Requirements for Manuscripts in April 2010 include *Annals of Internal Medicine*, *British Medical Journal*, *Canadian Medical Association Journal*, *Chinese Medical Journal*, *Croatian Medical Journal*, *Journal of the American Medical Association*, *Nederlands Tijdschrift voor Geneeskunde (The Dutch Medical Journal)*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *The Lancet*, *The Medical Journal of Australia*, *Revista Médica de Chile*, *Tidsskrift for Den Norske Lægeforening (The Journal of the Norwegian Medical Association)*, *Ugeskrift for Læger (Journal of the Danish Medical Association)*, the U.S. NLM, and the World Association of Medical Editors.

Although only a small number of journals compose the ICMJE, most reputable, peer reviewed journals (<http://www.icmje.org/journals.html>) follow their guidelines.

The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. Trial registration with missing fields or fields that contain uninformative terminology is inadequate.

It is important to note that the ICMJE requires registration of trial methodology but does not require registration of trial results; it recognizes the potential problems that could arise from the posting of research results that have not been subjected to an independent peer-review process. However, the ICMJE understands that the U.S. Food and Drug Administration Amendments Act of 2007 (FDAAA) does require researchers to register results. The ICMJE will not consider results to be previous publication if they are posted in the same primary clinical trial registry as the initial registration and if the results are posted in the tabular form dictated by the FDAAA. Researchers should be aware that editors of journals that follow the ICMJE recommendations may consider more detailed description of trial results and results published in registries other than the primary registry (in the case of FDAAA, ClinicalTrials.gov) to be prior publication. The ICMJE anticipates that the climate for results registration will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results registration.

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer to either the trial they are reporting or to other trials that they mention in the manuscript.

The ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry. The details of this policy are contained in a series of editorials (see Editorials, under [Frequently Asked Questions](#)). The ICMJE encourages editors of other biomedical journals to adopt similar policy.

Frequently Asked Questions about Clinical Trials Registration:

1. Will the ICMJE consider clinical trial results posted at ClinicalTrials.gov in compliance with the Food and Drug Administration Amendments Act of 2007 to be prior publication?

It is important to note that the ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require results reporting for registered trials. While the ICMJE recognizes the potential problems associated with posting preliminary research results that have not yet undergone an independent peer-review process, it acknowledges that the Food and Drug Administration Amendments Act of 2007 (FDAAA; U.S. Public Law 110-85, Title VIII), mandates the posting of summary results data for certain trials in ClinicalTrials.gov. Thus, the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication. The ICMJE anticipates that the climate for reporting results for registered trials will change dramatically over coming years and the ICMJE may need to amend these recommendations as additional agencies institute other mandates related to results reporting.

2. Does the ICMJE require registration of clinical trials of devices? What if I register my device trial in ClinicalTrials.gov and it is covered by the delayed posting (“lock box”) provision of

Food and Drug Administration Amendments Act of 2007 (FDAAA), meaning that the registered information is not publicly accessible immediately following registration?

The ICMJE does require public, prospective registration of clinical trials of all interventions, including devices. Two options are available to investigators who are conducting trials covered by the FDAAA lock box provision and seeking consideration for publication in ICMJE journals:

If you wish for the information to be made available to the public in accordance with the ICMJE clinical trials registration policy, do not answer the optional question, “Delayed Posting? (Y/N),” during the registration process that results in the placement of device trial registration in the lock box.

Alternatively, you may wish to register the trial in another acceptable registry, in addition to ClinicalTrials.gov. Although the ICMJE believes that dual registration should be avoided in most situations, it is, however, another mechanism around the ClinicalTrials.gov device trial lock box problem. Note that each registration should cross-reference the unique registration identification number (e.g., NCT number for ClinicalTrials.gov) issued by the other registry to ensure recognition that both registrations present information about a single device trial.)

3. Do trials that began before July 1, 2005 need to be enrolled before September 13, 2005 in order to be eligible for consideration at an ICMJE journal?

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. While the ICMJE hoped that all such trials would be registered by September 13, 2005, the committee understands that the policy statement was not entirely clear. Thus, ICMJE journals will consider trials that began before July 1, 2005 that were not registered prior to September 13, 2005. 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”).

4. What is the ICMJE definition of an “ongoing” trial?

The ICMJE considers trials that began enrollment before July 1, 2005 to be “ongoing” if the investigators were still collecting, cleaning, or analyzing data as of July 1, 2005. Ongoing trials require registration before submission to a journal.

5. What is the ICMJE definition of a clinical trial?

The most recent editorial on trials registration at www.icmje.org discusses the evolution of the ICMJE definition of clinical trials. In June 2007 the ICMJE adopted the WHO's definition of clinical trial: "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." 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. The ICMJE member journals will start to implement the expanded definition of clinically directive trials for all trials that begin enrollment on or after 1 July 2008. Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal. The ICMJE secretariat office is unable to review specific studies to determine whether registration is necessary. If researchers or others have questions about the need to register a specific study, they should err on the side of registration or consult the editorial office of the journal they wish to publish the study in.

6. What is the relationship between the ICMJE trials registration policy and the ongoing WHO trials registry effort?

In September 2005, the ICMJE implemented a policy that requires registration of clinically directive trials. The WHO is also working towards the implementation of an international trials registration process. Although several editors of ICMJE journals are independently involved as advisors to the WHO process, the two efforts are separate. The ICMJE welcomes the WHO initiative and is following its progress closely. When the final WHO policy is available, the ICMJE will determine whether to revise the ICMJE requirements to correspond to the WHO requirements. At present, the ICMJE expects investigators who wish to publish in ICMJE journals to adhere to the current ICMJE trials registry policy as documented on this web site (see May 2005 editorial and Frequently Asked Questions for details of the current ICMJE policy including the definition of applicable trials, acceptable registries, timing of registration, and required data items).

7. Which trials registries are acceptable to the ICMJE?

The ICMJE accepts registration in the following registries:

www.anzctr.org.au

www.clinicaltrials.gov

www.ISRCTN.org

www.umin.ac.jp/ctr/index/htm

www.trialregister.nl

In addition to the above registries, starting in June 2007 the ICMJE will also accept registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (see <http://www.who.int/ictrp/network/primary/en/index.html>). Because it is critical that trial registries are independent of for-profit interests, the ICMJE policy requires registration in a WHO primary registry rather than solely in an associate registry, since for-profit entities manage some associate registries. Trial registration with missing or uninformative fields for the minimum data elements is inadequate even if the registration is in an acceptable registry.

8. What should trial registries that wish to be ICMJE-acceptable registries do?

The ICMJE is no longer the entity that reviews registries for acceptability. Registries should consult the WHO International Clinical Trials Registry Platform. Registries that the WHO designates as primary registries will be acceptable to the ICMJE.

9. Where can I get information about how to register a trial?

Please refer to the registry that you choose to register in for instructions about the registration process for that specific registry.

10. I'm having trouble registering my trial in ClinicalTrials.gov or believe that my trial is not eligible for registration in that registry... What now?

Send an email to register@clinicaltrials.gov with your question or explaining the problems you are encountering.

11. Are clinical trials registries in languages other than English acceptable to meet the ICMJE's trials registration policy?

The ICMJE is cooperating with the WHO effort and will adopt WHO policy with respect to registry language. However, until the WHO has a mechanism in place to solve the problems of searching across registries in different languages, the ICMJE feels that the minimal data items need to be registered in English as well as in the native language of the registry.

12. Do I need to register a trial if the subjects were health care providers and not patients?

Some trials assign health care providers, rather than patients, to intervention and comparison/control groups. If the purpose of the trial is to examine the effect of the provider intervention on the health outcomes of the providers' patients, then investigators should register the trial. If the purpose is to examine the effect only on the providers (for example, provider knowledge or attitudes), then registration is not necessary.