Editorial

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Registration of Clinical Trials Still Moving Ahead – September 2008 Update to Uniform Requirements for Manuscripts Submitted to Biomedical Journals

The International Committee of Medical Journals' (ICMJE) policy on mandatory registration of clinical trials had made an important contribution to the transparency of clinical research even before it became a prerequisite for manuscript submission (1-3). Until recently, the scientific publication was the most detailed public record of the clinical trial, but reports in journals had been often burdened by selective reporting of trials and trial results, which very often distorted the evidence available for clinical decision-making (1).

The requirement for trial registration by the ICMJE member journals is built on the existing examples of public databases of clinical trials, such as the ClinicalTrials.gov registry. This information resource was established by the Food and Drug Administration Modernization Act on November 1997, as a registry of clinical trials "of experimental treatments for serious or life-threatening diseases or conditions" (4).

The most recent US legislation on mandatory registration of trial summative results, which came in effect on September 27, 2007, increased the transparency of clinical trials to an even higher level (5). As described in detail in the communication from the Director of the ClinicalTrials.gov registry (Box 1), the basic results of trials addressing drugs, biologics, or devices will have to be registered in the database within 12 months after the end of the trial. The basic results are formatted as tables of baseline characteristics, participant flow, outcomes, and adverse events. As of October 5, 2008 – a week after the law became effective, there were two trials with posted results, one from Denmark and one from California, US. Detailed guidelines and mock-up examples of formatting the results, including the statistical analysis are available at *http://prsinfo.clinicaltrials.gov/ResultsExamples.pdf*.

The latest legislature on trial results registration raised concerns among authors whether data registration constitutes a previous publication, so that a manuscript submitted to a journal would be a redundant publication. This was an important question for the ICMJE, which discussed it at the 2008 meeting in Philadelphia, USA. ICMJE reaffirmed that posting of trials results in a public database is not a publication as defined by its member journals, and this constitutes a major update in the Uniform Requirements for Manuscripts (URM) Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication.

The 2008 URM update carries the same definition of the redundant publication (section

Box 1. Update from ClinicalTrials.gov on mandatory registration of trial results in the USA (available at *http://www.icmje.org/clinicaltrials.htm*)

The National Library of Medicine has received questions concerning the posting of results at ClinicalTrials.gov (*http://clinicaltrials.gov*) in compliance with US Federal law and "prior publication" decisions by journal editors.

As you may know, US Public Law 110-85, Title VIII, mandates the submission of "basic results" data for certain clinical trials of drugs, biologics, and devices, effective September 27, 2008. The law applies to trials that are not Phase 1 or small device feasibility studies, and that have at least one site in the US, regardless of who sponsors, finances, or conducts the trial. Certain other trials may also be covered by the law. In general, these summary results data must be submitted within 12 months of the completion of data collection for the primary outcome measure. The law also requires submission of results for pre-specified secondary outcome measures registered at ClinicalTrials.gov. Delays in submitting results may be granted for certain reasons, but not generally for journal submission. There could be significant penalties for failure to comply with this law.

These "basic results" include summary data tables of baseline characteristics, participant flow, outcomes, and adverse events. With the exception of several brief free-text fields for providing descriptions of the data, no narrative information is included (eg, there is no discussion or conclusion section). There will be no patient level data.

The June 2007 ICMJE Update on Trial Registration (1) states that "the ICMJE will not consider results posted in the same primary clinical trials register in which the initial registration resides as previous publication if the results are presented in the form of a brief, structured (<500 words) abstract or table." The ICMJE recently reaffirmed this position at its 2008 annual meeting in Philadelphia.

Further, a January BMJ editorial (2) urges other journals to consider publication of results reported under the law to ClinicalTrials.gov for the following reasons:

First, disclosure will be a legal requirement, so there is nothing editors can do about it if they still want to publish important trials of drugs and devices. Moreover, journals will continue to add value by publishing useful and readable trial reports that clinicians, the media, and patients can interpret and use. And, most importantly, the results disclosed for the FDA will not have been externally peer reviewed and will be preliminary. Peer review not only provides a stamp of quality assurance, it often leads to reanalysis of results.

Please feel free to contact me if you have any questions about this new feature of ClinicalTrials.gov.

Sincerely,

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1. ICMJE. Clinical trial registration: looking back and moving forward. Jun 2007. Available at *http://www.icmje.org/clin_trial07.pdf*. Accessed on September 22, 2008.

2. Groves T. Mandatory disclosure of trial results for drugs and devices. BMJ. Jan 2008;336:170.

III.D.2. Redundant Publication) and its distinction from the trial results summaries in a registry: "The ICMJE does not consider results posted in clinical trials registries as previous publications if the results are presented in the form of a brief structured abstract or table. The results registry should either cite the full publication or include a statement that indicates that the report has not been published in a peer reviewed journal."

The distinction from the redundant publication and support for the registration of trial results is emphasized in the new paragraph of the 2008 URM update in the section III.J: „It is important to note that the ICMJE requires registration of trial methodology, but does not require registration of trial results. The ICMJE recognizes the potential problems that could rise from the posting of research results that have not yet undergone an independent peer review process. However, the ICMJE understands that the Food and Drug Administration Amendments Act of 2007 (FDAAA) in the United States does require researchers to register results. The ICMJE will not consider results posted in the same primary clinical trials registry as the initial registration 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 "Frequently Asked Questions" section now includes two new questions explaining the relationship between the new US legislation and the ICMJE requirements for trial registration, particularly the difference between the two for device trials (Box 2).

We urge the researchers involved in clinical trials to study the new registration requirements and remain aware that trial registration as a prerequisite for manuscript submission to a journal means that the trial has to be registered before the enrolment of the patients to the study (1-3). They also have to be aware of the change in the definition of a clinical trial, which ICMJE has implemented for studies registering after July 1, 2008 – a clinical trial is "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" (3).

These are exciting times for clinical research and its transparency, and it will be interesting to follow how the registration of trial results will be addressed globally. Those asking for more transparency will say that the most recent US legislation applies only to phase II to IV drug studies, excluding phase I trials which may provide important information on adverse drug reactions. Trials including surgical procedures, education, or psychological or dietary interventions are also not covered by the US legislation. But this is much more than what is currently available at the level of the European Union, which has still not opened its trial register, EudraCT (*https://eudract.emea.europa.eu/index.html*), to the public.

The trial registries and results databases have added public visibility to information beyond the scientific publication: trial existence,

Box 2. Questions about Clinical Trials Registration and Food and Drug Administration Amendments Act of 2007 (available from: *http://www.icmje.org/faq.pdf*)

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; US 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 (eg, NCT number for ClinicalTrials.gov) issued by the other registry to ensure recognition that both registrations present information about a single device trial.)

summary of protocol details, as well as summary of the results (5). The transparency of the full trial protocol and trial data sets are currently discussed as the next steps in achieving full transparency of clinical trials and informed health care decisions. Recently, the PROCTOR meeting (6) has opened an international dialogue of different constituencies interested in results reporting – clinicians, researchers, journal editors, representatives of consumers groups, policy makers, ethicist, public funders, layers, and systematic reviewers, with the aim to contribute to development of high international standards for results disclosure which will facilitate comparison and searching between different sources.

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