



Clinical trial disclosure— focusing on results

By Kathy B. Thomas and Claudia Tesch



Introduction

Clinical trial disclosure has reached a peak of activities over the last year and more promises to come during the next year. The activities around this topic deal with the prospective *registration* of *new* clinical studies and the retrospective disclosure of *results* for *completed* studies.

The original purpose of *clinical trial disclosure*, some 10 years ago, was to register clinical trials with serious and life-threatening diseases and conditions in a public domain (Internet) so as to provide an opportunity for patients and their physicians to locate a clinical study with new treatment options for their condition (FDAMA Section 113 of 1997) [1]. The original purpose was expanded in 2004 by the International Committee of Medical Journal Editors (ICMJE), who in an effort to curb the ‘positive results publication bias’, announced an unprecedented editorial publication policy that made public registration of clinical studies (not just those with serious and life-threatening diseases and conditions) at or before the start of patient enrolment a prerequisite for future publication of results in a growing number of peer-reviewed journals. The ICMJE policy became effective in September 2005 [2-4]. Additional impetus to *clinical trial disclosure* came from the pharmaceutical and medical trade associations [5], the general public and professional media [6-9], healthcare professionals, legislators worldwide, and healthcare consumers [10]. The latest activity occurred in September 2007, when the US congress updated the previous federal law dealing with *clinical trial disclosure* [1] and enacted a new law (Food and Drug Administration Amendments Act of 2007—FDAAA 801), which mandates the registration of *new* clinical studies and disclosure of results for *completed* studies [11].

In our contribution on *clinical trial disclosure* to *TWS* in June 2007, we covered the following topics: ·Background and chronological development, ·Stakeholders—their claims and recommendations, ·Implications of registry databases for *new* clinical studies, and ·Implications of results databases for disclosure of *completed* clinical studies [12]. Here, we summarise selected points of interest and milestones of the last 12 months and indicate some of the announced future directions of *clinical trial disclosure*. The focus here will be on *clinical trial disclosure* with regard to the newly enacted federal law FDAAA 801. We also indicate developments on this topic in other countries, although a complete overview of the international situation

is not possible at this stage, as many countries are still in the process of either establishing a national registry or investigating processes to align with other established registries. During this evolving phase, those who require information on national requirements regarding *clinical trial disclosure* need to seek instructions and guidance with the appropriate national health and regulatory authorities.

Prospective registration of new clinical studies

In the last 12 months, the registration of *new* clinical studies has been generally accepted and implemented by the pharmaceutical industry, universities, government affiliations, and other organisations involved in studies with human subjects. This can be deduced from the steady number of new user accounts and records for *new* clinical studies in the various clinical study registers [10], the largest of which are ClinicalTrials.gov (run by the National Library of Medicine of the US NIH; www.clinicaltrials.gov) and the ISRCTN (International Standard Randomised Controlled Trial Number) Register (administered by Current Controlled Trials Ltd; <http://isrctn.org/>) [8,13,14]. The registers provide a unique study identifier, which may be required as proof of study registration in a public domain for ethics committees, regulatory authorities, conference presentations, manuscript submissions to peer-reviewed journals, or when applying for research grants.

Ideally, new study information should only be entered into *one* register to avoid duplication and potential confusion. However, this is not always feasible because in some countries the national law or guidelines require national registration of clinical studies, often in the national language (e.g. Japan, Taiwan). Consequently, companies that perform international clinical studies will likely be obliged to register the study in the respective national clinical study register and additionally in an international register. The WHO International Clinical Trials Registry Platform (ICTRP) provides a search portal to locate trials from many primary registries worldwide (<http://www.who.int/ictrp/en/>). A similar service for ongoing and completed studies is available through the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) (<http://www.ifpma.org/clinicaltrials>).

FDA Amendments Act (FDAAA 801)

On 27 September 2007, the US Congress passed and enacted a federal law dealing with *clinical trial disclosure*—

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'FDAAA 801'[11]. The new law expands on the previous law (FDAMA Law, Section 113, 1997) [1] and covers topics of prospective registration of *new* clinical studies as well as retrospective results disclosure for *completed* studies.

The new law FDAAA 801:

- mandates prospective registration on ClinicalTrials.gov of *all new* controlled clinical investigations (other than Phase I) of drugs, biologics, and devices subject to regulations by the FDA;
- applies to research for *any* condition, regardless of sponsor type (industry, government, or academic) or location of conduct—if the products concerned need approval by the FDA;
- expands on the required mandatory information fields, being consistent with those of the ICMJE and the WHO [3,15];
- requires that *results* of *completed* clinical studies for FDA-approved or cleared medical drugs and devices be electronically available in a public register (linked to a registry entry as well as to any Medline citations of published results);
- specifies enforcement measures for non-compliance;
- is effective for *new* or *ongoing* studies from December 2007 (90 days after enactment) and for *completed* studies of approved medical products and devices from September 2008 (12 months after enactment).

Registry of new studies

Under the new law, the responsibility to register a *new* study lies with the sponsor or the principal investigator designated to conduct the study and having sufficient data rights. New clinical study must be registered within 21 days after the first patient is enrolled, updates of the registry information must occur at least every 12 months, and recruitment status should be updated within 30 days of any change. December 2007 was the due date to start registering *new* studies or updating all required information fields for *ongoing* studies.

After submitting information for drugs, biologics, and *approved* or *cleared* medical devices to the administrator (of ClinicalTrials.gov), the entries are usually publicly available (posted) on the Internet within 30 days. It is noteworthy, that unlike with therapeutic drugs and biologics, in the case of *new* clinical studies with medical devices *not* previously *cleared* or *approved* by the FDA, information submitted will be posted on the Internet only *after approval/clearance* by the FDA.

The basic elements for *registry* of *new* studies include:

- descriptive information (title, study design, primary/secondary outcome measures);
- recruitment information (eligibility, recruitment status);
- location and contact information (site-specific);
- administrative information (protocol number, IND/IDE, ethics committee vote).

Not all of the requested information is visible to the public (e.g. a copy of at least one ethics committee approval must

be provided but the details are not made public). The entries may be updated; version control is in place. The linguistic style of entries should be checked with communication experts to assure that there is no risk of patients or the lay public being misled.

Results disclosure of completed studies

The new law requires that results of *completed* clinical studies for FDA-approved or cleared medical products be electronically linked to the registry entry in the NIH register (www.clinicaltrials.gov) as well as to any Medline citations of published results. Results disclosure in other databases is not accepted (e.g. databases supported by the pharmaceutical industry or professional associations such as the Pharmaceutical Research and Manufacturers of America, PhRMA). In addition, certain agreements between the sponsor and non-employees, such as restrictions on the principal investigator to discuss or publish results after study completion, need to be declared.

The basic elements for *results* of completed studies include:

- demographic and baseline characteristics;
- number of dropouts (flow-chart);
- primary and secondary outcomes;
- point of contact;
- certain agreements (between the sponsor and the principal investigator).

Two models have been proposed for the presentation of the results: a structured narrative style and a tabular form, the tabular form being favoured. Results tables should be similar to those given in research articles; data can be edited or changed as necessary (with public tracking of changes). The challenge now is to determine the technical aspects for data entry that would suit all study types. The deadline for results disclosure is 12 months after study completion; the definition for study completion being '*last patient, last visit*'. Delayed disclosure of results (up to two years) is possible in exceptional cases, e.g. when national security interests are affected or if the sponsor can show that initial approval or a new indication or use for the drug or device is currently being sought. The due date to start posting results for *completed* studies for FDA-approved drugs or devices is 27 September 2008.

Enforcement measures for non-compliance

The new law specifies enforcement measures for non-compliance. Those who fail to comply will be fined \$10,000 for each infringement with no upper limit and in addition will be named in the non-compliance list posted on the ClinicalTrials.gov Internet site.

Future action points

The new law specifies further action points proposed to come into effect in March 2009. In addition to study registration and/or results disclosure, the sponsor will be required to collect and provide information on adverse

events of tested drugs and devices. This should include a table with *serious adverse events* (by system organ class, number and frequency, and study group) and a table with *frequent adverse events* (non-serious anticipated and unanticipated events occurring in >5% of patients within any study groups, by system organ class, number and frequency, and study group).

ICMJE

Registry of new studies

The ICMJE's position on the prospective registration of *new* clinical studies has remained unchanged since their last editorial in June 2007 [4]. The ICMJE, joined by other journal editors [16], require that in order to qualify for future publication "*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*" be registered in a non-profit register before enrolment of the first study subject. This requirement includes preliminary studies, e.g. Phase I, whereas purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration to qualify for future publication. However, registration of observational studies is required in some countries by national industry associations (e.g. Germany [17]). The latest ICMJE policy comes into effect for studies that start enrolment on or after 1 July 2008; studies that began before that date must be registered prior to editorial review [4]. This policy is being adopted by a growing number of journals, many of which are included in the list available on the ICMJE homepage <http://www.ICMJE.org> or by checking the 'Instruction for

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authors' in the journal of interest (<http://mulford.meduohio.edu/instr/>).

Results disclosure of completed studies

The international and legislative pressure to disclose results of completed studies in a timely manner has led to a potential conflict of interest regarding publication of clinical studies in peer-reviewed journals. The question has been raised as to whether editors would still want to publish previously disclosed data. For the present, the ICMJE has stated that results posted in the same clinical trials register in which the initial registration resides will *not* be considered as prior publication (prepublication) provided the results were only presented in the form of a brief (less than 500 words) structured abstract or table [4], and further solutions are being sought [18]. The next meeting of the ICMJE is planned for middle of June 2008 and the main topic of discussion is likely to be the alignment of the ICMJE requirements with the new US federal law on *clinical trial disclosure*—with focus on the study results disclosure and the various national requirements. An editorial on this meeting is eagerly awaited by all affected.

The WHO—international requirements—other than those included in the FDAAA law

The WHO proposals regarding *clinical trial disclosure* go even beyond the new US FDAAA 801 law. The WHO calls for *all* interventional studies (including early-phase studies such as Phase I) to be registered and information on results made public. Furthermore, the WHO promotes information on *new* clinical studies to be registered in national primary registers, thereby facing the dilemma of the language used for communication and reporting. The information is avail-

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Watch out for fake hamsters and eggs

A news item on the BBC reported that pet hamsters are banned in Vietnam. Their popularity as pets had been soaring partly due to 2008 being the Chinese Year of the Rat. The Ministry of Agriculture sees these imports from China and Thailand as a disease risk. The report goes on to say "The animals are just one of many imports that escape adequate scrutiny or epidemiological control in Vietnam. A recent survey alarmingly showed that most anti-malaria drugs—in Vietnam and other countries of the region—were fakes traced back to China". Does this mean there is a danger that the hamsters might be fakes too? This is not such a stupid question because the report further states "And reports abound of other counterfeit or dangerous items sold for human consumption—including rather startling internet rumours of a trade in fake chicken's eggs."

<http://news.bbc.co.uk/2/hi/asia-pacific/7283299.stm>

Identify your punctuation mark and vocabulary improvement

A blog where you can do the sort of 'tests' typical for teeny and women's magazines, e.g. 'Is he more than a friend?' is the sort of nonsense that is of no interest to us level-headed medical writers. But there is a blog that offers one test medical writers should ignore at their peril. What's more the answer and explanation I got on trying the test was remarkably accurate. Try for yourself at <http://www.blogthings.com/whatpunctuationmarkareyouquiz>

For something more addictive you can test your vocabulary for a good cause. The site owners state that they donate 20 grains of rice to the UN World Food Program every time you answer correctly. For 'Free Rice' go to <http://www.freerice.com/index.php>

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able through the WHO's International Clinical Trial Registry Platforms Search Portal (<http://www.who.int/trialsearch>) [15,19,20].

The WHO has just announced their first round of consultation processes aimed to promote reporting of clinical study results. A discussion paper on the topic has just been published in the WHO bulletin. Those interested in contributing to the discussion survey can do so, by 27 June 2008, at <http://www.who.int/ictrp/results/en/>.

Current requirements—worldwide

Currently, registration of *new* clinical studies is mandatory in the following countries: Argentina, Croatia, Israel, Italy, South Africa, Taiwan, and the USA. National guidance on voluntary registration exists in Australia, China, Germany, India, Japan, the Netherlands, New Zealand, Spain, and the United Kingdom. Proposed national laws are being discussed in several countries, including France. For other countries, no relevant reliable information was available to us at the time of writing.

With regard to results disclosure for completed studies, except for the USA (FDAAA 801), no other country in the world has a clear law mandating this aspect of *clinical trial disclosure*. Nevertheless, even within the United States, state law may take precedence over federal law as is the case in Maine—at least until the FDAAA 801 law is fully implemented in 2010 [12,21].

Final comments

The global situation with regard to *clinical trial disclosure* is changing and developing at a fast pace. This is sometimes at the expense of clarity and coordinated efforts of the stakeholders. The next 12 months will be the testing ground for results disclosure of completed clinical studies performed with approved products. Stakeholders such as the ICMJE, EMEA, WHO, and professional industry associations will have to align to reach an effective and agreeable solution. For those actively involved in preparing and disseminating medical and scientific information, as medical writers, this is an opportunity to make professional contributions to this cause.

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Affiliations/Competing interests

Kathy B. Thomas is an independent medical and scientific writer working on various projects from her office in Meersburg on Lake Constance, Germany. Claudia Tesch is an employee of Nycomed Deutschland GmbH, located in Konstanz, Germany. Both are well versed in coordinating entries for registers (new clinical trials and results of completed trials) applicable to *clinical trial disclosure*. Both have presented the topic and actively participate in professional international working groups dealing with this topic.

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