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By Elizabeth Wager

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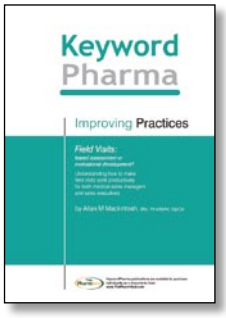

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FDAAA Legislation: Global Implications for Clinical Trial Reporting and Publication Planning

by Elizabeth Wager

Executive summary

The Food and Drug Administration Amendments Act (or FDAAA), which was passed in 2007, has major implications for drug companies that plan to market their products in the USA. Section 801 of the Act outlines the ways in which clinical trials need to be reported. Most notably, it makes registration and the public reporting of results mandatory for certain clinical studies, through the www.ClinicalTrials.gov website.

The legislation applies to all FDA-approved medical products licensed for use in the USA and for products that are due to be submitted for marketing approval to the FDA. All controlled clinical investigations other than phase I studies are covered by the Act.

Although FDAAA is US legislation, it is likely to have consequences far beyond the USA and may profoundly affect the ways in which clinical trials are reported and made public. The legislation has implications for the publication of clinical trial findings in peer-reviewed journals, as well as for the clinical trial registers recognised by the International Committee of Medical Journal Editors.

This report, *FDAAA Legislation: Global Implications for Clinical Trial Reporting and Publication Planning*, describes the requirements for trial registration and the reporting of results, and explains what companies need to do now. Since the legislation is open-ended, and several aspects will not come into force for the next couple of years, the report also analyses future implications and highlights currently unanswered questions.

The first phase of FDAAA implementation, with elements governing clinical trial reporting, was due to come into force in late September 2008. Despite its US focus, it is clear that, globally, companies need to have systems in place to ensure they comply with this new legislation.

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Elizabeth (Liz) Wager is a member of the World Health Organization (WHO) Scientific Advisory Group on trial registration, the CONSORT statement group, the *BMJ*'s Ethics Committee, and the World Association of Medical Editors Ethics Committee. She is Secretary of the Committee on Publication Ethics and a Visiting Fellow of the UK Cochrane Centre. She is a regular peer-reviewer for several journals including the *BMJ*, the *Journal of Medical Ethics, PLoS Medicine* and *JAMA*.

After obtaining a First Class zoology degree from Oxford in 1983 she worked for Blackwell Scientific Publications, Janssen-Cilag then Glaxo-Wellcome. In 2001, she set up her own company, Sideview, which provides training, writing, editing and publication consultancy services. She has advised numerous drug companies and communication agencies about trial registration and publication policies, and has run workshops on five continents.

Liz has written books on '*Getting Research Published: an A to Z of Publication Strategy*' and '*How to Survive Peer Review*'. She is a co-author of '*Good Publication Practice for Pharmaceutical Companies*' and the European Medical Writers Association guidelines on the role of medical writers.

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FDAAA Legislation: Global Implications for Clinical Trial Reporting and Publication Planning

What is FDAAA?

FDAAA – an unwieldy abbreviation that I've heard called 'fe-daah' and 'F-D-triple-A' – stands for the Food and Drug Administration Amendments Act of 2007. It is also called Public Law 110-85. The act amended the US Public Health Services (PHS) Act. It should not be confused with the FDA Modernization Act (FDAMA), which was passed in 1997. FDAAA covers several areas including prescription drug user fees at the Food and Drug Administration (FDA), paediatric research, postmarketing surveillance and even the safety of pet food. This report focuses on how FDAAA affects the ways in which clinical trials need to be reported; these fall under Section 801 of the Act.

What led to FDAAA?

The phenomenon of publication bias started to receive attention with the growth of evidence-based medicine and the increasing importance of systematic reviews, such as those produced by the Cochrane Collaboration.[1] Until then, most published studies had been viewed singly, but when all the evidence about a treatment was put together (in the process of compiling systematic reviews), it became clear that positive findings were more likely to be published than negative ones. For academic studies, positive studies are those that favour a particular hypothesis or that achieve statistically significant results, whereas for commercially funded studies they are those that favour the sponsor's product. Several studies showed evidence of systematic bias, with drug companies, in particular, being accused of suppressing inconvenient findings.[2,3] Companies were also shown to be inflating the evidence of the efficacy of their products by publishing positive findings more than once in ways that made it hard to spot the redundancy.[4,5] Research suggested that the non-publication of negative studies and the double-counting of positive ones were skewing the outcomes of meta-analyses.[6] This led to calls that trials should be registered.[2,7,8]

Registering clinical trials before they start has several benefits (at least from the viewpoint of systematic reviewers and journal editors):

- it provides information about studies that never get published
- it enables redundant publications to be identified (if the trial registration number is included on publications)
- it can highlight selective or misleading reporting by providing a record of the key outcomes agreed at the start of the trial, which can be compared against reports of the findings.

Researchers have been calling for trial registration since the mid-1980s[7] and FDAMA (the predecessor of FDAAA, which was passed in 1997) required the registration of efficacy trials in 'serious and life-threatening diseases'. However, this legislation was not strongly enforced and was largely ignored. Nevertheless, the passing of FDAMA did lead to the creation of the ClinicalTrials.gov register in 1998 by the US National Library of Medicine (NLM) of the National Institutes of Health (NIH), although it only began to accept online filings in 2000.

Meanwhile, many drug companies remained opposed to trial registration. In 2002, the US industry association, Pharmaceutical & Research Manufacturers of America (PhRMA), stated in its guidelines on trial reporting: "Sponsors do not commit… to make the designs of clinical trial protocols available publicly at inception, as in a clinical trial registry".[9]

The Good Publication Practice guidelines for pharmaceutical companies (published in 2003) called on companies to endeavour to publish results of all clinical trials of marketed products.[10] Again, this requirement met with opposition.[11] However, in 2004, the members of the self-appointed but highly influential International Committee of Medical Journal Editors (ICMJE) decreed that in future they would not publish studies unless they had been prospectively registered.[12,13] This led to a dramatic increase in the number of registrations.[14]

The tough stance of the ICMJE (which includes the editors of the world's largest journals such as *The Lancet* and the *New England Journal of Medicine)* also led to a dramatic change in the policy of the PhRMA, which, in 2004, announced: "The pharmaceutical industry has committed to registering information about all new and ongoing clinical trials… in a free, publicly accessible clinical trial registry."[15] Many smaller journals followed the lead of the ICMJE, and several companies made public commitments to register at least some of their trials.[16]

Another factor that made drug companies reconsider the wisdom of not publishing all their clinical trials, at least of their marketed products, was the lawsuit brought against GlaxoSmithKline (GSK) by the New York Attorney General in 2004.[16,17] GSK stood accused of "persistent fraud" for failing to publish negative results about its anti-depressant paroxetine (sold in the US as Paxil® and in Europe as Seroxat®). The case was settled out of court but GSK, in addition to paying a settlement of $2.5 million, agreed to make all its study results public in future. More recently, Merck has faced much media criticism and costly lawsuits

relating to its handling and publication of trial information about rofecoxib (Vioxx®).[18]

These events set the scene for the US Congress to pass FDAAA in 2007, making registration and the public reporting of results mandatory for phase II–IV trials of all FDA-approved medical products and those due to be submitted for marketing approval to the FDA. Although the Act was passed in September 2007, the sections relating to results' reporting began to come into effect a year later (i.e. September 2008).

FDAAA: requirements for 2008

The website www.ClinicalTrials.gov was set up in 1998 as a trial register – to record design details of trials, largely entered before patients are recruited. FDAAA extends the role of ClinicalTrials.gov to include a database of results. This is generally referred to as the 'basic results database'. (It is important to distinguish this official US government-backed website from another website that reports clinical study results, run by the PhRMA – www.ClinicalStudyResults.org.) In the legislation itself, it is simply referred to as the 'results data bank' – this will no doubt mutate into an abbreviation or acronym sometime soon! The term 'basic' has probably been adopted to indicate that the scope of the database is set to expand.

Which products are affected?

The new legislation applies to all FDA-approved medical products (i.e. drugs and devices licensed for use in the USA) and to products that are due to be submitted for marketing approval to the FDA (i.e. all drugs and devices aimed at the US market).

Which trials are affected?

The new legislation relates to 'applicable clinical trials', which are defined as controlled clinical investigations other than phase I studies. Single-arm or observational studies, and preclinical trials, are not included.

Compulsory trial registration

FDAAA extends compulsory trial registration to phase II–IV trials for all diseases. Under the previous FDAMA, registration was required only for trials of serious or life-threatening diseases. The Act sets out the information that should be posted on the register – this is based on the World Health Organization (WHO) minimum dataset for trial registration (Table 1). On ClinicalTrials.gov, this function is referred to as the 'Protocol Registration System' or PRS. This is slightly confusing, since the trial register contains considerably less detail than a full protocol, and posting of full protocols is not envisaged for several years.

Registering a trial on ClinicalTrials.gov automatically generates a trial identifier called the National Clinical Trial (NCT) number, which must now be included in submissions for marketing approval to the FDA.

FDAAA	WHO minimum dataset
Unique protocol ID number	Primary register and trial ID #
Other protocol ID numbers	Secondary ID #s
FDA IND number and date	
	Source(s) of monetary or material support
Name of sponsor	Primary sponsor
	Secondary sponsor(s)
Responsible party/Point of contact	Contact for scientific queries
Brief title (for public)	Public title
	Scientific title
Lay summary	
Facility name and contact info	
Primary purpose	
Disease or condition studied	Health condition(s) or problem(s) studied
Outcomes (including primary and secondary)	Primary outcome(s)
	Key secondary outcomes
Intervention name and type	Intervention(s)
Access for unlicensed drugs?	
Study type Study design	Study type
Study phase	
Eligibility criteria	Participant characteristics
Gender, age limits, ?healthy volunteers	
Recruitment status	Recruitment status
Individual site status	Countries of recruitment
Start date	Date of first enrollment
Expected completion date	Estimated date of final measurement/visit
Target number of subjects	Target sample size

Table 1. FDAAA requirements for trial registration and WHO-recommended minimum dataset for trial registers.

Timing

Trial registration

Applicable trials that started after 27 September 2007 must be registered on ClinicalTrials.gov within 21 days of the first patient being enrolled. On-going trials for serious or life-threatening diseases should have been registered within 90 days of FDAAA enactment (i.e. 27 December 2007), whereas on-going trials for all other conditions should have been registered within 1 year of FDAAA enactment (i.e. 27 September 2008).

The posting of results

The timing limits for the posting of results depend on the status of the product being studied. For new (i.e. unlicensed) drugs, trial results must be posted within 30 days of either marketing approval or of the

FDA issuing a notice of non-approval. In other words, whatever the outcome of the licence application, results must be posted within 30 days of an FDA decision. Results must also be posted if a marketing application is submitted but then withdrawn and not resubmitted within 210 days.

For studies of licensed medicines in their licensed indications, results must be reported within 12 months of either the estimated or the actual trial completion date, whichever is earliest

For studies of licensed medicines falling within their licensed indications, results must be reported within 12 months of either the estimated or the actual trial completion date, whichever is earliest. The completion date is defined as the date on which the final subject was examined or received an intervention for the purposes of the final collection of data for the primary outcome. It makes no difference whether a trial runs to its planned conclusion or is stopped earlier than anticipated – results must still be posted within 12 months.

However, trials of new indications of licensed products (i.e. phase IIIb trials) need not be posted according to this schedule, but are treated like studies of unlicensed treatments (i.e. they must be reported within 30 days of the new indication being approved, or after the FDA issues an action letter rejecting the submission, or if the marketing application is withdrawn).

This means that the results of most clinical trials will be made publicly available, regardless of whether the trials result in FDA approvals.

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What results must be posted?

The Act defines four elements for posting basic results. These are:

- demographic and baseline characteristics
- primary and secondary outcomes
- contact details
- statement about any restrictions on publishing the results.

Worked examples for parallel-group, crossover studies and diagnostics trials are available from ClinicalTrials.gov. Some of these are used to illustrate specific posting requirements in the following sections.

	Drug A	Drug B	Placebo	Total
Number of participants [units: participants]	50	50	50	150
Age [units: participants]				
<=18 years	0	0	0	0
Between 18 and 65 years	50	50	50	150
>=65 years	0	0	0	0
Age [units: years] Mean ± standard deviation	41 ± 12	42 ± 11	41 ± 11	41 ± 11
Gender [units: participants]				
Female	25	23	28	76
Male	25	27	22	74

Table 2. Worked example of a table showing patient demographics, taken from ClinicalTrials.gov.

Demographic and baseline characteristics

Demographics must include participants' age and gender (Table 2). Other details such as race and region of enrolment are optional. Demographic details and baseline characteristics for the entire study population and for each trial arm must be shown.

The flow of patients who participated in the clinical trial through the trial must also be shown in a table (see Table 3). This should indicate:

- the number of patients recruited
- the number of patients who dropped out
- the number who were excluded from the analysis.

	Drug A	Drug B	Placebo
STARTED	50	50	50
COMPLETED	48	49	47
NOT COMPLETED	2	1	3
Lost to Follow-up	1	0	2
Adverse Event	1	1	1

Table 3. Worked example of a table showing participant flow through a study, taken from ClinicalTrials.gov.

The Act's definition of "patients who participated in the clinical trial" is vague, and fails to specify whether this means the number recruited, those found eligible or those who were randomised.

ClinicalTrials.gov explains that including participant flow is "identical in purpose to a CONSORT diagram, but represented as tables"

ClinicalTrials.gov explains that including participant flow is "identical in purpose to a CONSORT diagram, but represented as tables". Trial 'milestones' (or phases) can be defined by the user. The number of patients starting and completing each milestone period must be entered, along with reasons why participants did not complete a particular phase.

Reasons for not completing a study phase are categorised as:

- adverse event
- death
- lack of efficacy
- lost to follow-up
- physician decision
- pregnancy
- protocol violation
- withdrawal by subject
- other (which should be specified).

Outcomes reporting

The primary and secondary outcomes, as prespecified in the trial register, must be described along with "results of scientifically appropriate tests of the statistical significance of such outcome measures". The study arms and details of the comparator groups are copied automatically from the protocol section, but they can be changed when results are entered.

	Drug A	Drug B	Placebo
Number of participants [units: days] Log mean ± standard deviation	50	50	50
Time to disease X [units: days] Log mean ± standard deviation	4.94 ± 1.32	5.52 ± 1.28	4.78 ± 1.11

Table 4. Worked example of a table showing the analysis of the outcome measure, time to disease, taken from ClinicalTrials.gov.

The outcomes tables can accommodate categorical, continuous and time-to-event data. The number of patients analysed for each outcome measure in each arm must be reported (Table 4). Information about how the analysis group was determined (e.g. 'per protocol' or 'intention to treat') is optional.

Outcomes must be identified as primary or secondary (both prespecified in the protocol section), other prespecified outcomes and post-hoc outcomes. There is also a question about whether the outcome measure assesses a safety issue. At present, this field is not compulsory but it has been added in order to comply with FDAAA.

At present, the field 'Statistical analyses' is optional, but this information is likely to be required in future.

Groups	All groups
Method	ANOVA
P value	0.011

Groups	Drug A vs. Drug B
Method	t-test, 2 sided
P value	0.017
Mean difference (Net)	-0.672
95% Confidence interval	(-1.224 to -0.119)

Table 5. Worked examples of tables showing statistical analyses for the outcome measure, time to disease X, taken from ClinicalTrials.gov.

This is likely to include whether a superiority or non-inferiority analysis was performed and methods of any statistical tests used. In a presentation, Deborah Zarin, who coordinates the ClinicalTrials.gov programme at the NLM, suggested that statistical information should include details of the following (see Table 5):

- which groups were being compared
- the names of the tests used to produce any p-values (e.g. chi-squared, ANOVA)
- effect size, such as odds ratios or risk ratios
- estimates of variance such as 95% confidence intervals.

There is an optional field for 'Overall limitations and caveats', which may be used to describe limitations of a trial such as technical problems or early termination.

Contact details

Contact details for obtaining further scientific information about the trial need to include either a named individual or a position title (e.g. Clinical Trials Director) together with their phone number and email address.

Control over the dissemination of results

FDAAA describes details about the sponsor's control over publication as "Certain Agreements". These are designed to show the existence of any agreement between the sponsor and the principal investigators – who are not company employees – that restricts the freedom of the principal investigators to present or publish the results of a clinical study. There are three categories of agreements:

1. The sponsor can review documents and embargo them for up to 60 days while they are being reviewed (but cannot change presentations or submissions).
2. The sponsor can review documents and embargo them for between 60 and 180 days (but cannot change presentations or submissions).
3. Any other restriction on disclosure (e.g. if the sponsor has the right to require changes or can veto a communication).

Who should do the posting?

The Act refers to the "responsible party", which it defines as the sponsor of a clinical trial or the principal investigator if designated for this role by the sponsor. This simply means that the sponsor is responsible for registering the study and posting results. ClinicalTrials.gov is set up only to accept postings from registered users, so in practice, this usually means somebody at the drug company. This system was adopted to limit the number of people ClinicalTrials.gov needs to interact with and because it was felt that it would be simpler to go back to a single point of contact if there were queries. For investigator-initiated studies, companies should agree with the principal investigator who will be responsible for registration and reporting.

Penalties for non-compliance

Failure to comply with the Act can lead to fines of up to $10,000, and, if the problem is not corrected within 30 days, then fines of up to $10,000 per day can be imposed until the posting is corrected. These penalties apply to late postings and also to false or misleading postings.

Failure to comply with the Act can lead to fines of up to $10,000 per day

Future requirements of FDAAA

Adverse event reporting (2009)

FDAAA requires information about adverse events to be reported in the second phase of implementation, starting from late September 2009. Until then, such information is optional and the methods of reporting adverse events may evolve. The Act requires the NLM to "determine the best method for including… appropriate results information on serious adverse and frequent adverse events… in a manner that is useful and not misleading to patients, physicians, and scientists". The systems are to be developed by March 2009 and should come into force by September 2009.

FDAAA requires information about adverse events to be reported in the second phase of implementation, starting from late September 2009

As of October 2008, the reports database suggests that sponsors should report serious adverse events (grouped by organ system, including numbers and frequencies for each arm of the trial) and other adverse events that exceed an (unspecified) frequency threshold in any arm of the trial. The worked example (Table 6) shows adverse events that occurred in at least 5% of participants. At present, any standard terminology system for coding adverse events (such as Medical Subject Headings [MeSH], Systematized Nomenclature of Medicine [SNOMED] or Medical Dictionary for Regulatory Activities [MedDRA]) can be used (but the system should be specified). Organ systems are prespecified on the database.

Serious adverse events are defined as "events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, a persistent or significant disability/incapacity or a congenital anomaly/birth defect".

The number of affected participants, the number of events and the number of participants at risk (i.e. the number assessed) should be described for each event (see Table 6).

	Drug A	Drug B	Placebo
Total over all other adverse events number of participants affected	16	4	13
Gastrointestinal disorders Nausea number of participants at risk number of events number of participants affected	 50 4 4	 50 2 2	 50 2 2

Table 6. Worked example of a table showing adverse event reporting (with a frequency threshold of 5%), taken from ClinicalTrials.gov.

Lay summaries (2010)

Consumer groups have been supportive of trial registration and many advocate greater transparency for results reporting. However, there is also concern that websites that report results could be used to promote products inappropriately (e.g. for off-label indications) or might present misleading information to the public. FDAAA therefore makes provision for the reports of results to include summaries "written in non-technical, understandable language for patients", but also includes a caveat that this will be required only if suitable systems can be developed to ensure that such summaries are not "misleading or promotional". NIH employees state that this phase is planned for 2010.

Summaries written in "non-technical, understandable language for patients" maybe required by 2010 so long as these are not promotional

Posting full protocols

FDAAA also makes provision to require full protocols to be made available, but does not specify the timing for this. Some groups have argued that the information about a trial's conduct and design that is included in a trial register is insufficient, and have therefore encouraged the publication of full protocols. For example, this is a requirement of the Ottawa Statement.[19]

Quality control for results posting

Some commentators have raised concerns that FDAAA will result in a proliferation of unchecked and potentially misleading information about clinical trials becoming available on public websites. At present, the accuracy and quality of information posted on trial registers or results databases is the responsibility of whoever enters the data (in most cases the sponsor). Large companies are likely to have their own quality-control mechanisms, but there is, at present, no independent scrutiny or peer review.

FDAAA makes provision for a "pilot quality control project" to "determine the optimal method of verification to help to ensure that the clinical trial information… is not false or misleading". However, the Act gives no further details or hints about what sort of system might be put in place. Routine peer-review or quality checking of all postings would be time-consuming and therefore costly. Although ClinicalTrials.gov received some additional funding under FDAAA, it was rumoured that it did not receive as much as it had hoped for, and certainly not enough to extend its remit to include scrutinising postings more thoroughly. Randall Lutter, the FDA Deputy Commissioner for Policy, has said that the implementation of the Amendments Act presents numerous challenges. Writing on the FDA website, he said: "It's a bit like remodeling a kitchen while continuing to cook in it", and has admitted that some deadlines have not been met. This suggests that resources are currently stretched. In the absence of any further resources being pumped into the system, it seems unlikely that an exhaustive system of routine review will be established. Instead, automatic quality control measures – such as computer systems that prevent registrants from entering illogical data or leaving fields blank – or random audits may be employed.

In future, when trials are included in submissions for marketing authorisation, these must be accompanied by certification that the trial was appropriately registered and reported. For trials that are funded by the NIH (and certain other US federal agencies), the funding agency must certify that the trial has been properly registered and reported.

Consultation and rulemaking

The NIH/NLM has been consulting with invited groups of experts (including drug company employees) during 2007/8 and has also posted dummy data tables for comment. FDAAA requires that a public meeting must be held no later than March 2009 "to provide an opportunity for input from interested parties". Once workable systems have been developed (e.g. for results and adverse event posting) these will be formalised by a process known as rulemaking. The Notice of Proposed Rulemaking (NPRM) for the expanded trial registry is due to be circulated for comments in autumn 2008.

Implications of FDAAA

Drug companies need to respond to FDAAA legislation in a number of ways and put systems in place to ensure they comply with it.

- Registration of study design details needs to occur within 21 days of the first patient enrolment. Some Research Ethics Committees now demand that trials are registered before they will approve them, so, in practice, this may occur considerably earlier.
- Companies need to have systems in place to ensure that trial registration is performed correctly and in accordance with FDAAA. Although it is not clear how much the FDA will police such entries, some journals are now checking registration details and have refused to publish studies that were not registered properly (e.g. if they were registered after the trial began or if insufficient details were supplied).[13]
- Companies that previously registered their trials on registers such as the International Standardized Randomized Controlled Trial Number (ISRCTN) system or national registers should review their policies to check that they comply with FDAAA. ClinicalTrials.gov is currently the only register set up to accept the results summaries that are required by the Act.
- Patient consent forms for trials that will be included in licence applications to the FDA should indicate that the trial has been (or will be) registered in accordance with FDAAA.
- Since trial results must be posted within 12 months of the estimated trial completion date (even if the actual completion date is later), companies should be careful when estimating trial end dates.
- Since the trial completion date is defined in terms of assessment of the primary outcome, this may influence treatment or examination schedules. For example, if the last assessment of the primary outcome (i.e. an efficacy measure) occurred several weeks before the final assessment for another outcome (such as quality of life or health economics) then this would effectively reduce the time available to prepare data for postings. This is because the clock starts ticking after the final visit for the primary outcome regardless of other, subsequent data collection points.
- Companies may wish to review their investigator agreements regarding their right to review and embargo documents. FDAAA does not actually limit what companies can do, but the distinction between embargoes of up to 60 days and those of between 60 and 180 days may make companies alter their policies so that they fall into the less restrictive category.

Other factors companies need to be aware of

How does FDAAA affect individual state legislation (e.g. Maine)?

The US state of Maine issued its own rules,[20] which became effective in March 2007, requiring drug manufacturers to publish results of "hypothesis-testing clinical trials of FDA-approved drugs" on a publicly accessible website. This applied to all drugs available in Maine and for all trials that started after 15 October 2002. FDAAA includes a clause which means that it overrides

such laws from individual states. However, the Governor of Maine issued a letter on 14 September 2008[21] explaining that "the Maine statute and rule requiring clinical drug trial registration and results reporting remain in force and are not yet pre-empted by federal statute". According to the Governor, "Until federal rules are adopted that fully implement federal requirements for results reporting, Maine's requirements remain legally enforceable". In other words, the Maine requirements for registration and posting will remain in force until the results reporting requirements of FDAAA are fully implemented and formally codified into federal rules (rather than the current draft guidance).

Since Maine passed its law several months before ClinicalTrials.gov launched its results database, companies had to use alternatives such as their own corporate websites or ClinicalStudyResults.org (hosted by the PhRMA) to issue the data required. From 8 December 2008, Maine will recognise only results posted on ClinicalTrials.gov as complying with the state legislation. Companies that posted trial results on other websites (to comply with the Maine law) do not have to re-post them. However, according to the Governor's letter, "Maine encourages manufacturers to re-post such results and anticipates considering the adoption of such a requirement in future rule-making".[21]

What impact will FDAAA have outside the USA?

There are no signs that European regulators (i.e. the European Medicines Agency [EMEA]) intend to follow the FDA and require either public registration of trials or the posting of results. The EMEA has been criticised for holding back trial registration initiatives by keeping its own European Union Drug Regulating Authorities Clinical Trial (EudraCT) database – which contains details of every trial submitted as part of a licensing application – confidential.[8] However, European pharmaceutical industry associations (in line with their US and Japanese counterparts) have broadly accepted trial registration.

In 2006, the European Union (EU) passed a law about paediatric medicines (EU 1901/2006)[22] requiring that some details on paediatric studies included in the EudraCT database be made public. A consultation document was issued in March 2008. Commentators suggest it is unlikely that this partial opening up of the EudraCT register will lead to complete openness, so a comprehensive pan-European trials register seems unlikely.

The Association of the British Pharmaceutical Industry (ABPI) has publicly supported trial registration for several years[23] although it has not required its members to register all their studies. However, the ABPI now requires that studies used to make advertising claims in the UK must be registered. The ABPI has also issued a statement (in June 2008)[24] about the reporting of results, recommending that companies follow the structure of clinical trial report summaries given in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E3 guidelines.[25] This format is far less structured than the tables required by ClinicalTrials.gov but has been used by many companies that post results on their own websites. The ABPI best practice model recommends that results should be presented "in a format which is clear, concise and easily understood by patients and the general public". The ABPI paper comments that although the ICH-E3 template is "easy to use", it does not necessarily make the results "easy to understand". The ABPI best practice model, while setting out some laudable goals, does not appear to take into consideration the requirements of either the FDAAA or the ICMJE.

How will result posting affect publication in medical journals?

Editors of peer-reviewed journals will generally not accept reports of findings that have been published previously. When some drug companies first announced plans to post their trial results – in response to the lawsuit against GSK in New York in 2004 – there was concern that such policies might prevent publication in peer-reviewed journals. At that time, it appeared that journals lacked a consistent policy on whether they would accept results that had previously been posted.[26]

However, in June 2007, the ICMJE issued an 'Update on Trial Registration'[27] which stated 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." According to the ICMJE website, the ICMJE reaffirmed this position at its 2008 annual meeting in Philadelphia.

In the Frequently Asked Questions section of the ICMJE website, the committee states: "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."

Interestingly, the ICMJE's Uniform Requirements – which have been endorsed by hundreds of journals, not just the ICMJE members – make no mention of the 500-word limit, but simply state: "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". If the 500-word limit were to be strictly policed, this might cause problems, but a quick word count on the sample tables for a parallel-group trial suggest that these can be completed

quite comfortably within the 500-word limit (the worked examples from ClinicalTrials.gov shown in this review include about 430 words). There is also no mention that trials must be registered and reported in the same register.

At present, posting results on ClinicalTrials.gov will not jeopardise full publication in a journal

When the ICMJE made its initial announcement in 2004 about requiring trial registration as a condition for publication,[12] it appeared that only ClinicalTrials.gov met the journal editors' criteria. However, soon afterwards, this position was revised, and the ISRCTN switched from a commercial to a not-for-profit provider and was recognised by the editors as an appropriate location for registering trials. However, the ISRCTN does not currently support the reporting of results.

Companies that have registered their trials in registers other than ClinicalTrials.gov may have to re-register them in order to be able to post the results to meet the FDAAA requirements.

Some journal editors have highlighted the fact that posted results will not be peer-reviewed (in contrast, of course, to reports in their own journals). An editorial in the *BMJ* noted that "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 re-analysis of results".[28]

This raises a possible source of confusion and disagreement, by suggesting that results appearing in peer-reviewed journals will sometimes be different from those posted on the FDAAA database, if different analyses are done in response to reviewers' comments. ClinicalTrials.gov currently provides links from register entries to PubMed publications but it is not clear what will happen if findings are disputed or whether results can be corrected or updated.

Effects on other trial registers

At present, ClinicalTrials.gov is the only major trial register that is equipped to include results. FDAAA (unsurprisingly, being US legislation) clearly assumes that trials will be registered and reported in ClinicalTrials.gov. However, the ICMJE recognises several other public registers, such as the ISRCTN scheme. In order to publish in the major medical journals, there is no specific requirement that trials must be registered in ClinicalTrials.gov – some other registers (e.g. the Japanese, Dutch and Australian national registers) are acceptable – nor that results should be posted.

FDAAA requirements, combined with the ICMJE's suggestion that trials should be registered and results reported in the same registry, are likely to increase the dominance of ClinicalTrials.gov, which is already the world's largest trial register.

Other trial registers have recently been, or are being, developed – for example, German, Indian and Chinese registers were launched in 2008. Most appear to be waiting to see how FDAAA is enacted before deciding whether to follow ClinicalTrial.gov's example of extending its remit to include the reporting of results.

The WHO was influential in developing an internationally recognised minimum dataset for trial registration, which most registers now follow (see Table 1). The WHO guidelines are also mentioned specifically in FDAAA. However, the WHO has not developed guidance on how results should be reported.

Some unanswered questions

If companies decide only to post results on a website such as ClinicalTrials.gov and not to publish in a traditional journal, several questions arise which, so far, appear to have received little attention.[29]

It is not clear how entries in databases should be cited or whether such citations are acceptable in publications or promotional material. Logically, a publicly accessible posting would seem to be a step beyond 'data on file' – which can be used in some countries, such as the UK, to support promotional claims. In other countries with stricter marketing guidelines (e.g. where abstracts may only be used up to 1 year after the meeting) it is unclear what status results postings will be accorded.

Since academic promotion depends on publication in peer-reviewed journals, it seems likely that large and interesting studies will continue to be published in the traditional format. More routine studies may simply be posted on databases rather than being submitted to journals. However, if companies come to view results posting as a replacement for publication in journals, issues of authorship and acknowledgement may arise. The systems proposed under FDAAA do not include space to list investigators nor the possibility of acknowledging a study team or writing group. Only a single contact person is listed – and that is likely to be somebody from inside the sponsoring company. If academics want recognition for their contributions to studies, a system of authorship will need to be devised. The authorship of papers in traditional journals is fraught with difficulties and sometimes contested,[30] so it will be interesting to see what effect anonymous results posting might have.

FDAAA legislation is open-ended on the issues of the publication of full protocols, the best method for reporting adverse events that occur in trials and the desirability (and possible format) of publishing summaries of results aimed at the general public. People

responsible for trial registration and compliance with FDAAA will need to stay alert for new developments.

FDAAA has major implications for any drug company that plans to market its products in the USA

Conclusions

FDAAA has major implications for any drug company that plans to market its products in the USA. All phase II–IV clinical trials should be registered on ClinicalTrials.gov and companies need to establish systems for reporting trial results to comply with the new legislation – broadly speaking, within a year of study completion for trials of marketed products or within 30 days of a decision about licensing, positive or negative, from the FDA for new products or new indications. Companies also need to keep abreast of the unfolding phases of FDAAA implementation, which will probably include adverse event reporting (in 2009) and lay summaries (by 2010). In addition, those involved with publication planning need to stay alert for guidance from journal editors about whether certain types of results posting will prevent later publication in peer-reviewed journals. At present, it appears that posting results using the ClinicalTrials.gov tabular format will not jeopardise full publication in a journal.

However you pronounce it, FDAAA is likely to be more rigidly enforced than FDAMA and cannot be ignored.

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Increasing Transparency in Pharmaceutical Marketing Communications: the new code from the European Federation of Pharmaceutical Industries and Associations (EFPIA)

A KeywordPharma **Expert Review** by Joan Barnard, Rene Lai and Andrew Robson — Published February 2008

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A line-by-line summary of all revisions, both major and minor, to the latest EFPIA codes, offering insight into the likely implications for the pharmaceutical industry and its customers.

Executive Summary

The representative body of the pharmaceutical industry in Europe, the European Federation of Pharmaceutical Industries and Associations (EFPIA), issued the latest revision to its code of practice in late 2007. The EFPIA code, introduced in 1992 and last revised in 2004, does not act as a pan-European code, but is implemented through the national codes of its member organisations. The updating of these national codes in line with the new EFPIA guidelines will be completed by the end of July 2008.

Prompted by a desire to answer growing criticism of the pharmaceutical industry with a robust and effective system of self-regulation, the new EFPIA code aims to foster an environment where the public can be confident that choices regarding the medicines they are prescribed are based on individual merits and healthcare needs. As such, the need for greater transparency in pharmaceutical marketing communications is the main take-home message from the new code, which comprises revisions and clarifications designed to tighten existing regulations.

Despite this, certain aspects of the code remain open to interpretation, while other areas allow for flexibility in implementation.

This Expert Review delivers a line-by-line summary of all revisions, both major and minor, to the EFPIA code, and offers insight into the likely implications for the pharmaceutical industry and its customers. It outlines the background and principles of the new code, looks at how it will work in practice and provides guidance on its implementation.

The Review also includes details of an entirely new, separate EFPIA code, designed to regulate industry relationships with patient organisations.

In both cases, the latest EFPIA guidelines underline an increased desire for clarity and transparency in how the industry interacts with its healthcare customers.

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About the author

Dr Joan Barnard (www.joanbarnard.co.uk) is the author and publisher of 'The Code in Practice', a practical guide to the ABPI Code for Head Office staff, and 'The Code in the Field', a guide to the ABPI Code for Medical Representatives. Both books are now in their third editions and are used widely throughout the pharmaceutical industry.

Joan joined the pharmaceutical industry in 1980 and held various positions in clinical research and medical affairs, both in the UK and internationally, including 5 years as a UK Medical Director. She was a member of the ABPI Code of Practice Appeal Board for 4 years.

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