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CRS Report for Congress

Clinical Trials Reporting and Publication

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Clinical Trials Reporting and Publication

Summary

The central issue before Congress with respect to clinical trials reporting and publication is how to balance the potential beneficial public health effects of requiring that clinical trials data be made public with the burdens that such requirements may place on companies and their innovation. Clinical trials, which are conducted regularly to test the effects of new pharmaceuticals and medical devices, cost a significant amount of money, and by their nature may present some risk to the people who participate in them. Manufacturers as well as medical journal editors have been reluctant to publish clinical trial data indicating that products in development are harmful or ineffective. The availability of such information might save a duplication of effort and studies that harm or fail to help patients.

While current federal regulations require the publication of some clinical trials data, and some private entities have taken steps to encourage publication, there is no requirement that the public have access to all standardized clinical trials data — be it notice of trial launch or research results through a centralized system such as a registry. Food and Drug Administration (FDA) regulations require sponsors of trials that test the effectiveness of new drugs for serious or life-threatening conditions to register with the Department of Health and Human Services (HHS) at [http://clinicaltrials.gov/], although not all such trials are listed there. Clinical trial data from National Institutes of Health (NIH)-funded research may be made public through a Freedom of Information Act request only if the findings were used by the federal government in developing an agency action that has the force and effect of law. The International Committee of Medical Journal Editors (ICMJE) requires, for publication of clinical trial results, that a sponsor have posted its trial in a public registry before enrolling patients. A voluntary registry of recent controlled trials results was created in October 2004 by the Pharmaceutical Research and Manufacturers of America (PhRMA).

Proposals for public access to all or most clinical trial data raise a variety of issues. These relate to the goals of providing public access, the appropriateness of the information and its presentation for the audience, the timing of a trial's inclusion, whether reporting should be mandatory, potential conflicts of interest, and whether medical device trials should be included.

Eight relevant bills have been introduced during the 110th Congress. One, the Fair Access to Clinical Trials (FACT) Act (S. 467), would require the registration of clinical trials, some of which must currently be registered at [http://clinicaltrials.gov], and the subsequent posting of their results. The act would also make public certain information about FDA's non-approval actions, which is currently not required to be released. Seven other bills, the Food and Drug Administration Revitalization Act (S. 1082), the Enhancing Drug Safety and Innovation Act of 2007 (S. 484 / H.R. 1561), the Food and Drug Administration Safety Act of 2007 (S. 468 / H.R. 788), and the Pediatric Medical Device Safety and Improvement act of 2007 (S. 830 / H.R. 1494) also contain provisions about clinical trials reporting and publication.

This report will be updated on a regular basis.

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Clinical Trials Reporting and Publication

Introduction: Current Federal Regulations

In 2004, Congress and others raised questions about the safety and effectiveness of several FDA-approved biomedical products on the market. These included certain antidepressants, Merck's pain relief drug, Vioxx, Boston Scientific's cardiac stents, and other drugs and medical devices. Discussion about ways to help ensure safety and effectiveness of biomedical products focused primarily on two questions: whether data from all clinical trials should be made publicly available, and whether FDA's processes for product approval and post-market surveillance and study are adequate. This report focuses on the first of these questions.[1]

The central issue before Congress with respect to clinical trials reporting and publication is how to balance the potential beneficial public health effects of requiring that clinical trials data be made public with the burdens that such requirements may place on companies and their innovation. On one hand, companies may lose a competitive advantage if their competitors are alerted to their clinical trials activities and failures. On the other hand, the public may be harmed if a particular type of clinical trial is repeated — particularly if an earlier trial demonstrated that a product was ineffective or harmful. In addition, if clinical trial data are to be made public, the timing and contents of the disclosure may prove to be pivotal, both with respect to competitive innovation and public safety.

Clinical trials reporting can mean public access to results after a trial's conclusion, to a proposed plan before a trial is begun, or both. There is no centralized system for either type of reporting; thus, different trials may have the same title, one trial may be reported in several places under different titles, and many trials are never reported. Researchers have traditionally reported pre- and post-market trial results in peer-reviewed medical journals, which have historically tended to favor publication of clinical trials demonstrating successful intervention; the results of negative or inconclusive trials often go unpublished.[2] Other venues for the dissemination of research results are industry, government, or university press releases and presentations at medical conferences. Researchers — who may be affiliated with a product's manufacturer, a university, the government, or an association established to find better treatments for a particular disease — may have various motives for publishing or not publishing results. Some observers have

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[1] For further information about whether FDA's processes for product approval and post-market surveillance and study are adequate, see CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul.

[2] "Pressure Mounts for Clinical Trial Registry," *Medicine & Health*, vol. 58, no. 24 (June 21, 2004), pp. 2-3.

expressed concern that a lack of transparency, particularly for negative data, could adversely affect medical decision-making.[3]

The lack of transparency may be amplified in part by sponsors' contractual requirements of their researchers. This concern was raised by two May 2005 medical journal articles, suggesting that contractual "gag" clauses might prohibit clinical trial investigators from examining data independently or submitting a manuscript for publication without first obtaining the consent of trial sponsors. According to one of the articles, sponsors with a financial interest in the outcomes of clinical research could thus suppress negative results and interfere with the publication of unfavorable data on safety.[4] The other article, which described results from a survey of medical school research administrators responsible for negotiating clinical trial agreements with industry sponsors, reported that industry provides approximately 70% of funding for clinical drug trials in the United States.[5] The survey results suggested that 85% of the administrators' offices would not approve provisions that gave industry sponsors the authority to revise manuscripts or to decide whether results should be published. Administrators' responses varied regarding whether contracts could contain provisions allowing sponsors to insert their own statistical analyses in manuscripts, draft manuscripts, or prohibit investigators from sharing data with their parties after the trial's conclusion.

In order to fully understand the debate surrounding clinical trials reporting and publication, a basic understanding of clinical trials themselves and of the current federal requirements — both of which are presented below — is essential. The slate of issues that frequently arise during discussions of clinical trials reporting and publication, all of which are addressed below in the "Issues" section of this report, include questions related to the goals of publication, the materials' appropriateness and presentation, the timing the disclosures, whether disclosure should be voluntary or mandatory with penalties, overcoming potential conflicts of interest, and whether medical devices should be included in reporting requirements.

Clinical trials are the gold standard. Clinical trials, which are the gold standard for assessing drug and device safety and effectiveness both before and after they are marketed in the United States, are scientific studies that systematically test interventions on human beings. They may include behavioral studies or other biomedical investigations, such as those that test drugs and medical devices. As described by FDA, clinical trials are generally conducted in four phases following successful animal testing.[6] Phase I trials study a new drug or device in a small group

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[3] Robert Steinbrook, "Public Registration of Clinical Trials," *JAMA*, vol. 351, no. 4 (July 22, 2004), p. 315.

[4] Robert Steinbrook, "Gag Clauses in Clinical-Trial Agreements," *New England Journal of Medicine*, vol. 352, no. 21 (May 26, 2005), p. 2160.

[5] Michelle Mello, et al., "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry," *New England Journal of Medicine*, vol. 352, no. 21 (May 26, 2005), p. 2202.

[6] For further information on the role of federal agencies in evaluating biomedical products, (continued...)

of people (20-80) to evaluate its safety, determine a dosage range for drugs, and identify gross side effects. Phase II trials study the product in a larger group of people (100-300) to see whether it is effective for a specific purpose and to further evaluate its safety. Phase III trials investigate the product in a large group of people (1,000-3,000), to confirm the product's effectiveness, monitor side effects, and collect information that will allow the drug, treatment or device to be used safely. Phase IV trials are usually large-scale studies, conducted after the FDA approves a product for marketing in order to demonstrate effectiveness in a broader clinical context and to watch for rare side effects that may not be identified until significant numbers of people have used the product.

Federal regulations require the publication of certain clinical trial information and encourage the disclosure of some results. The federal government has historically regulated certain aspects of some clinical trials by attaching conditions to those conducted with federal research funds, and/or by creating requirements that must be met before a drug or device can be marketed in the United States. Most federal funding occurs through the Department of Health and Human Services' (HHS) National Institutes of Health (NIH). According to NIH's regulations issued pursuant to a provision in the Omnibus Consolidated and Emergency Supplemental Appropriations Act, 1999 (P.L. 105-277), research data relating to published research findings produced under an award that were used by the federal government in developing an agency action that has the force and effect of law — a limited number of research results if any — must be released if a Freedom of Information Act request is made.[7]

Beginning in May 2005, the NIH has requested that investigators with manuscripts that are accepted for publication, and that are the result of research supported in whole or in part with direct costs from NIH, submit them voluntarily to the National Library of Medicine's (NLM's) PubMed Central.[8] (The NLM, which is located on the NIH campus in Bethesda, Maryland, is the world's largest medical library.) This effort would enables free access to results published elsewhere and would not facilitate access to previously undisclosed results. The NIH announcement was preceded by a July 2004 House committee recommendation that NIH provide free public access to the complete text of articles and supplemental materials generated by NIH-funded research.[9]

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[6] (...continued)
see CRS Report RS21962, *From Bench to Bedside: The Role of Health and Human Services (HHS) Agencies in the Evaluation of New Medical Products,* by Michele Schoonmaker.

[7] *Uniform Administrative Requirements for Grants and Agreements With Institutions of Higher Education, Hospitals, and Other Non-Profit Organizations; Final Rule (Office of Budget Management, Circular A 110)*, Federal Register, Vol. 65, No. 52, Page 14406 (March 16, 2000), at [http://grants2.nih.gov/grants/policy/a110_fed_reg_20000316.pdf].

[8] National Institutes of Health, "Policy on Enhancing Public Access to Archived Publications Resulting from NIH-Funded Research," NOT-OD-05-022, February 2, 2005, at [http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html].

[9] U.S. Congress, House Committee on Appropriations, *Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations Bill, 200*5, report to
(continued...)

Both pre-market approval and post-market monitoring of medical drugs and devices marketed in the U.S. are the responsibility of HHS's FDA. Each FDA center that reviews and approves biomedical products for human use — the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Biologics Evaluation and Research — posts summaries of safety and effectiveness data from clinical trials that support *approved* applications for new products, or new uses of approved products; FDA does not otherwise post clinical trials data.

The FDA Modernization Act of 1997 (FDAMA, P.L. 105-115, Section 113) required the Secretary of HHS to establish a clinical trials registry, intending the availability of information to increase the access of individuals to cutting-edge medical care available only through research protocols. Sponsors of trials testing the effectiveness of life-threatening disease or condition treatments (drugs, but not devices) that are being conducted to obtain FDA approval for marketing,[10] under an expanded use protocol[11] of an investigational new drug application to FDA, or on Group C[12] cancer drugs are required to register. In addition, any trial (drug, device, or other) that has been approved by a human subject review board (or equivalent) and conforms to the regulations of the appropriate national or international health authority may also be included.

In response to FDAMA, the NLM established a clinical trials registry and made it available to the public in 2000 [http://clinicaltrials.gov]. It was later reported that an FDA analysis found that in 2002 only 48% of trials of cancer drugs had been registered, and a preliminary review indicated the listing rate for drugs for some other serious diseases is in the single digits. Some companies had reportedly listed no studies; some trials were listed without identifying the sponsoring company or the drug being tested.[13] In March 2002, FDA issued a guidance document, instructing

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[9] (...continued)
accompany H.R. 5006, 108th Cong., 2nd sess., H.Rept. 108-636 (Washington, GPO, 2004).

[10] Pursuant to 21 U.S.C. § 355(i).

[11] An expanded use protocol is one that allows for widespread patient access to an investigational new drug not yet approved for marketing, when the drug has shown promise for treating a serious or life-threatening condition, there is no comparable or satisfactory alternative therapy, and the sponsor is actively pursuing permission to market the drug (21 U.S.C. § 360bbb(c)).

[12] Group C "was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols." *Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators,1998 Update, Drugs and Biologics*, FDA, at [http://www.fda.gov/oc/ohrt/irbs/drugsbiologics.html].

[13] Shankar Vedantam, "Drugmakers Prefer Silence on Test Data," *Washington Post*, July 6, (continued...)

industry how and when to participate in the registry [http://www.fda.gov/cder/guidance/4856fnl.htm].

A 2005 survey conducted by FDA's Office of Special Health Issues indicated that 67% of companies required to register their trials had done so.[14] The 2005 survey results were not comparable to those of 2002 due to methodological differences. It was reported that FDA did not plan to continue to monitor whether companies registered beyond 2006.[15]

In a July 2004 announcement unrelated to [http://clinicaltrials.gov/], the FDA announced that clinical trial sponsors could use a standard format, the Study Data Tabulation Model (SDTM) developed by the nonprofit organization Clinical Data Interchange Standards Consortium (CDISC), to submit clinical trials data to the agency [http://www.cdisc.org/index.html]. While the data would not necessarily be made public, according to the FDA, providing a consistent framework and format for clinical trial information is expected to enhance data integration opportunities and thereby reduce data management barriers for sharing the latest clinical trial data.[16]

Non-Federal Activities

A number of national and international groups recommended that clinical trial reporting be centralized, standardized, and/or include both positive and negative results, and have taken steps toward that goal.

World Health Organization (WHO) promotes trial registry standards, portal, and registration of all clinical trials. In May 2006, the WHO, the United Nations specialized agency for health which supports and funds much of the international research on marginalized populations, began urging research institutions and companies to register all medical studies that test treatments on human beings, including the earliest studies, whether they involve patients or healthy volunteers.[17] This dovetails with another WHO initiative: the International Clinical Trials Registry Platform (ICTRP), which aims to standardize the way information on medical studies is made available to the public. As a part of the ICTRP, WHO has

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[13] (...continued)
2004, p. A 1.

[14] "FDAMA Section 113: Status Report on Implementation," FDA Office of Special Health Issues, August 2005, at [http://www.fda.gov/oashi/clinicaltrials/section113/113report/default.htm], visited January 17, 2007.

[15] "FDA to Stop Tracking Industry Compliance With Clinical Trial Registry," *Inside Washington Publishers*, September 26, 2006.

[16] "FDA Announces Standard Format That Drug Sponsors Can Use to Submit Human Drug Clinical Trial Data," *FDA News*, July 21, 2004, at [http://www.fda.gov/bbs/topics/news/2004/NEW01095.html].

[17] "The World Health Organization announces new standards for registration of all human medical research," *World Health Organization website*, May 19, 2006, [http://www.who.int/mediacentre/news/releases/2006/pr25/en/index.html], visited January 18, 2007.

recommended that 20 key details — such as title, funding source, research ethics review, and outcome measures — be disclosed at the time studies are begun, that a Universal Trial Reference Number be assigned to each trial, and that minimum standards for the reporting of trial results be defined. (See **Appendix A** for a complete list of key details.) As the ICTRP progresses, WHO plans to launch a one-stop Search Portal for searching compatible registries worldwide.[18]

Some organizations have voiced opposition to the WHO efforts. The Pharmaceutical Research and Manufacturers of America (PhRMA) has reportedly opposed publicizing information early in the clinical trial, arguing that disclosing early research data does little to help doctors and patients, and may impede innovation by alerting competitors to companies' activities.[19] For similar reasons, the Advanced Medical Device Medical Technology Association (AdvaMed) has reportedly attempted unsuccessfully to allow device firms to delay disclosure of some required data elements.[20] AdvaMed argued that the issue was more pronounced for device than drug manufacturers because device development process is iterative, involving improvements over a period of time.

Since April 2004, all clinical trials approved by the WHO ethics review board have been required to be registered at their outset and assigned a unique identification number.[21] A London-based group of biomedical publishing companies agreed to maintain a no-charge, online register of these numbered trials at [http://www.controlled-trials.com] to identify and track them throughout their life cycle. The system was designed to avoid the problem of publication bias by posting information on trial starts and their results.

The International Committee of Medical Journal Editors (ICMJE) Clinical Trial Publication Policy requires registration. The ICMJE consists of the editors of 12 major journals, including the *New England Journal of Medicine*, *The Lancet*, and the *Journal of the American Medical Association*. In order for a sponsor to have its clinical trial results published in one of the ICMJE journals, the ICMJE requires it to have posted its trial in a public registry before enrolling patients.[22] The policy applies to any trial that started recruiting human subjects on or after July 1, 2005. The ICMJE did not advocate any particular registry, but cited

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[18] "International Clinical Trials Registry Platform" *World Health Organization website*, May 19, 2006, [http://www.who.int/ictrp/en/], visited January 18, 2007.

[19] "PhRMA Opposes UN Plan for Trial Data Disclosure," *Inside Washington Publishers*, May 30, 2006.

[20] "AdvaMed, WHO at Odds Over Global Trial Registry Standards," *Inside Washington Publishers*, July 19, 2006.

[21] Gerd Antes, "Registering clinical trials is necessary for ethical, scientific and economic reasons," *Bulletin of the World Health Organization*, May 2004, vol 82, no. 5., at [http://www.who.int/bulletin/volumes/82/5/en/321.pdf], visited January 18, 2007.

[22] Catherine De Angelis et al., "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors," *New England Journal of Medicine*, vol. 351, no. 12 (September 16, 2004), p. 1250, at [http://content.nejm.org/cgi/content/full/351/12/1250].

[http://clinicaltrials.gov/] as the only database currently meeting its requirements. In June 2005, the ICMJE specified the minimum set of data elements necessary for a trial to be considered fully registered, adopting the WHO list of 20 items.[23]

American Medical Association (AMA) recommends a comprehensive clinical trials registry. In an effort at dovetailing with the ICMJE requirements, in December 2004, the AMA House of Delegates committed the organization to take all appropriate action to protect the rights of physician researchers to present, publish, and disseminate data from clinical trials.[24] In June 2004, the AMA recommended that HHS create a comprehensive, centralized clinical trials registry. The AMA further called on all institutional review boards to make registration in this database a condition of their approval of the bioethical aspects of clinical trials.[25] Noting the AMA's position, Senators Tim Johnson and Christopher Dodd called for a national clinical drug trial registry in a July 8, 2004 letter to the heads of NIH and FDA.[26]

The Association of American Medical Colleges (AAMC) develops principles for clinical trials reporting. In January 2006, the AAMC Executive Committee approved a set of principles designed to promote standards for analyzing and reporting the results of sponsored clinical research.[27] The principles include, among other things, that researchers have an ethical obligation to make their results public, that contracts with sponsors should require a good-faith effort to publish results, and that trials should be fully registered according to ICMJE standards within 21 days of their outset either in [http://clinicaltrials.gov/] or elsewhere.

The Institute of Medicine (IOM) supports mandatory trial registration and results reporting. The IOM, a National Academies institute, conducted a workshop on developing a national clinical trials registry.[28] Workshop

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[23] Catherine DeAngelis et al., "Is This Clinical Trial Fully Registered?: A Statement from the International Committee of Medical Journal Editors," *New England Journal of Medicine*, vol. 352, no. 23 (June 9, 2005), p. 2436, and [http://www.icmje.org/clin_trialup.htm].

[24] American Medical Association, "610. Physicians and Clinical Trials," December 2004 Resolutions, at [http://www.ama-assn.org/meetings/public/interim04/resolutions.pdf].

[25] Joseph M. Heyman, "AMA Encouraged by Early Signs of Industry Support for National Clinical Trials Registry," *American Medical Association*, press release, June 18, 2004, at [http://www.ama-assn.org/ama/pub/category/13909.html].

[26] "Senators Call for National Registry of Clinical Drug Trials," Senator Tim Johnson, press release, July 8, 2004 [http://johnson.senate.gov/~johnson/releases/200407/2004708B20.html].

[27] Susan Ehringhaus and David Korn, "Principles for protecting Integrity in the Conduct and Reporting of Clinical Trials," *Association ofAmerican Medical Colleges*, January 6, 2007, at [http://www.aamc.org/research/clinicaltrialsreporting/clinicaltrialsreporting.pdf], visited January 18, 2007.

[28] Committee on Clinical Trials, Institute of Medicine of the National Academies, *Developing a National Registry of Pharmacologic and Biologic Trials* (Washington, DC:

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participants presented a range of views on the need for registries, registry content, implementation issues, and next steps. A separate draft publication published by IOM in 2006 recommended that Congress require industry drug sponsors to register phase 2-4 clinical trials at [http://clinicaltrials.gov/], and that initial postings be supplemented by a summary of safety and efficacy results.[29]

The pharmaceutical industry favors limited, voluntary clinical trial registration and reporting. The pharmaceutical industry's reaction to clinical trials reporting has been mixed, although as litigation and FDA and congressional interest have increased, some individual manufacturers and groups have volunteered to make some of their clinical trials data public. How the industry defines the types of trials to include (e.g., hypothesis-testing or late-phase only) could affect a registry's utility. Initially skeptical, PhRMA introduced its own clinical trials database in October 2004 at [http://www.clinicalstudyresults.org]. Companies that market drugs in the United States can voluntarily post the positive and negative results of controlled trials (mainly Phase III and IV studies) completed after October 2002 on the PhRMA database. As of April 16, 2007, 60 companies had posted results for 343 drugs. According to FDA, more than 10,000 drugs are approved for marketing in the United States. In January 2005, PhRMA additionally called for its members to voluntarily post all hypothesis-testing clinical trials on NLM's registry, clinicaltrials.gov.

In January 2005, an international pharmaceutical federation of which PhRMA is a member, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), announced that its members would voluntarily disclose summary results of all industry-sponsored clinical trials.[30] Trial results would be published in a standard, non-promotional summary that would include a description of trial design and methodology, results of primary and secondary outcome measures described in the protocol, and safety results. In October 2005, IFPMA announced that it had launched a search portal of clinical trial registries and databases worldwide.[31]

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[28] (...continued)
The National Academies Press, 2006), at [http://books.nap.edu/catalog/11561.html#toc], visited January 18, 2007.

[29] Committee on the Assessment of the US Drug Safety System, Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public, Advance Copy, Tuesday September 26, 2006*, (Washington, DC: National Academies Press, 2006), at [http://books.nap.edu/books/0309103045/html], visited January 18, 2007.

[30] The announcement was made jointly with PhRMA, the European Federation of Pharmaceutical Industries and Associations (EFPIA), and the Japanese Pharmaceutical Manufactures Association (JPMA). International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), "Global Industry Position On Disclosure of Information About Clinical Trials," *IFPMA Press Release*, January 6, 2005, at [http://www.ifpma.org/News/NewsReleaseDetail.aspx?nID=2205].

[31] IFPMA, "IFPMA Improves Biomedical Data Transparency with Launch of First Worldwide Clinical Trials Portal," *IFPMA Press Release*, September 21, 2005, at (continued...)

Legislation

A number of bills related to clinical trials reporting and publication have been introduced in the 110th Congress. One bill is solely focused on clinical trials registration and reporting: S. 467, the Fair Access to Clinical Trials (FACT) Act, introduced by Senator Dodd. Similar legislation was introduced in the 109th Congress by Senator Dodd (S. 470) and Representative Waxman (H.R. 3196), and in the 108th Congress by Senator Dodd (S. 2933) and Representative Markey (H.R. 5252).

Seven other bills introduced in the 110th Congress have components relevant to clinical trials reporting and publication. These bills have been primarily focused on drug safety and FDA reform. The Food and Drug Administration Reauthorization Act (S. 1082), introduced by Senator Kennedy, is composed of titles on the topics of reauthorizing the Prescription Drug User Fee Act, promoting drug safety, and encouraging the development of pediatric medical drugs and devices. One subtitle of the drug safety provisions would create a clinical trial registry and a clinical trial results database. The Enhancing Drug Safety and Innovation Act of 2007 (S. 484 and H.R. 1561), introduced by Senator Enzi and Representative Waxman, is composed of titles designed to address the following topics at FDA: risk evaluation and mitigation strategies, the Reagan-Udall Institute for Applied Biomedical Research, clinical trials, and conflicts of interest. The clinical trials title of each bill contains provisions that would create a clinical trial registry and results database. Although many provisions of S. 484 and H.R. 1561 are identical, those related to clinical trials reporting and publication are different.

Two other pieces of legislation with provisions related to clinical trials reporting and publication are the identical companion bills S. 468 and H.R. 788, the Food and Drug Administration Safety Act of 2007, introduced by Senator Grassley and Representative Tierney. The act would establish a Center for Postmarket Evaluation and Research for Drugs and Biologics at FDA. It would enable the Center Director to require certain pre- and post-market studies, and would require the HHS Secretary to make information about those studies available to the public.

The remaining two bills with provisions related to clinical trials reporting and publication are the pediatric Medical Device Safety and Improvement Act of 2007 (S. 830 / H.R. 1484) introduced by Senator Dodd and Representative Markey. The bills would expand tracking of FDA pediatric device approvals, modify and tighten the humanitarian device exemption (which waives user fees associated with the FDA's review of medical device applications), require the NIH Director to designate a point of contact to assist those seeking funding for pediatric device development, create demonstration grants for improving pediatric device availability, amend regulations governing the office of pediatric therapeutics and the pediatric advisory committee, and enable the Secretary to order certain postmarket studies as a condition of approval of pediatric medical devices. The bills would also require the HHS Secretary, acting through the FDA Commissioner, to establish a database of

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[31] (...continued)
[http://www.ifpma.org/clinicaltrials.html], visited April 27, 2007.

clinical trials on pediatric devices. The database would include trials conducted in conjunction with the aforementioned postmarket studies, or with FDA premarket device approval, clearance, or qualification as for the humanitarian device exemption.

Details of five proposals for clinical trials reporting and publication contained in S. 468 / H.R. 788, S. 467, S. 1082, S. 484 and H.R. 1561 are discussed in the text that follows, and compared with current law in **Table 1**. Due to the narrow scope of the proposal for clinical trial publication contained in S. 830 / H.R. 1484, it is not incorporated into the text or table. For purposes of this report, the repository of clinical trial information submitted at the outset of the trial is referred to as a *registry*, and the repository of the trial conclusions is referred to as a *results database*.

Registry. *Current law: Only trials that meet all three of the following criteria must be included in the registry, clinicaltrials.gov: (1) The trial is testing a drug; (2) The trial is being conducted to obtain FDA approval for marketing, is conducted pursuant to an expanded use protocol of investigational new drug application to FDA, or is conducted on a Group C cancer drug; and (3) The trial tests treatments of serious or life-threatening conditions. Other trials that have been approved by a human subject review board (or equivalent) and conform to the regulations of the appropriate national or international health authority may also be included.*

Each of the legislative proposals would expand the scope of the current law, which requires only the registration of certain drug trials, to include trials related to biologics as well. All but S. 484 would also require the inclusion of medical device trials. S. 467 would also allow for the results of other types of trials to be voluntarily submitted. All but S. 467 would also expand the registry to include trials beyond those for the treatment of life-threatening diseases or conditions.

Results Database. *Current law: there is no requirement that the results of clinical trials be made publically available, except those included as a portion of what FDA publishes upon its approval of an application.*

Most of the bills (all but S. 1082) would require public disclosure of study results. S. 1082 would require the NIH Director to issue a report and HHS Secretary to create a rule based on that report regarding the best way to make clinical study results available to the public.

Issues

Issues surrounding the possibility of clinical trials reporting and publication have focused on a range of topics. Those topics are discussed below, with an accompanying analysis of the clinical trials reporting and publication provisions contained in S. 467, S. 1082, S. 484, H.R. 1561, and S. 468 / H.R. 788.

Goals. Proponents of public access to clinical trials data cite the need to provide information to members of the general public, health care workers, and researchers, both to help inform treatment decisions and to help eliminate abuses. Industry advocates have also cited the potential benefits of public awareness of the resources necessary to get a drug approved, and the elimination of duplicated failed efforts. PhRMA cites making clinical trial results for U.S.-marketed pharmaceuticals

more transparent, and providing information to practicing physicians and their patients. Each of the legislative proposals aims to make information available and understandable to members of the public.

Appropriateness/Presentation. Some have questioned whether registration and publication of clinical trials and their results are the best mechanism for ensuring patient safety, both because the language may be too technical for lay audiences, and because numerous trials may need to be viewed together in order to draw meaningful conclusions — an analysis that would be difficult for many doctors as well. (A single clinical trial may generate thousands of pages of documentation.) These questions have led some to focus on how information might be presented in an audience-appropriate way. PhRMA's registry contains a link to drug labels, a bibliography, and a summary of results in a format developed by industry consensus.[32] All of the bills would contain information accessible to both the general public and professionals. Two, S. 484 and H.R. 1561, have the additional specific requirement that the results database contain both a technical and a nontechnical summary report, which might meet the differing requirements of professionals and lay persons.

Timing. Some have argued that only clinical study results are important to judging effectiveness, so publication of a trial's inception is not necessary. Others have argued that some registration at inception is necessary to avoid abuse, and is helpful for connecting potential subjects with various trials. FDAMA requires that notice of a qualifying trial be submitted to [http://clinicaltrials.gov/] no later than 21 days after the trial is open for enrollment. PhRMA's database only accepts results from completed trials. S. 467 and S. 1082 would generally require registration within 21 days that a trial is opened for enrollment. S. 484 and H.R. 1561 would require enrollment within 14 days after the first patient is enrolled. S. 467 / H.R. 788 would require that information about the study be posted not less frequently than every 90 days. For results submissions, S. 467 and H.R. 1561 would require them to be submitted within one year of the earlier of the trial's actual or estimated completion date. S. 484 would require results submissions not later than one year after the last patient has his or her last medical visit, and S. 467 / H.R. 788 would require results to be submitted upon completion of the study. All the bills except for S. 467 / H.R. 788 would allow for extensions for results submission in certain circumstances, such as when publication in a peer-reviewed journal is pending. S. 467 / H.R. 788 may also allow for such extensions by nature of the fact that the Director of the act-created Center for Postmarket Evaluation and Research for Drugs and Biologics would determine the studies completion date, and might therefore be capable of delaying the date if presented with good cause.

Voluntary or Mandatory/Penalties. Concerns about the potential regulatory burden on smaller drug and device manufacturers, as well as about the potential for intellectual property problems, have led some to call for voluntary registration and publication. The desire to protect public safety and to reduce abuse has led others to back mandatory reporting. PhRMA's registry is voluntary. The reporting proposed

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[32] *Structure and Content of Clinical Study Reports; Guideline Approved by the International Conference on Harmonization*, July 1996, at [http://www.fda.gov/cder/guidance/iche3.pdf].

in all of the bills would be mandatory (with limited exceptions for trials not conducted on drugs, devices, or biological products and those completed before the bill's enactment) and would carry penalties for noncompliance.

Conflicts of Interest. Some commentators have focused on the need for public disclosure of financial and other arrangements between researchers and sponsors in order to demonstrate potential conflicts of interest that may affect clinical trial design, interpretation of data, and presentation of results. The PhRMA database does not include information about funding relationships, though products there are identifiable by company, which may also be the trial funding source. All of the bills would require the disclosure of funding source(s), among other things.

Devices. Some have questioned whether information about clinical trials related to medical devices should be included in the registry. The medical device advocacy group, Avamed, points out that FDA regulation of devices is different from its regulation of drugs. Devices are often approved based on analytical comparisons to existing products rather than on the conduct of new clinical trials. Devices as compared to drugs often tend to present a lower risk to patients, tend to be manufactured by smaller companies, tend to have a short market life due to frequent, incremental refinements rather than major breakthroughs, and tend to require more financial incentives to test. PhRMA's database contains only information related to drug trials; those proposed in all of the bills except S. 468 / H.R. 788 would include trials related to medical devices. S. 467 / H.R. 788 would require the HHS Secretary, in consultation with the FDA Commissioner, the Director of the Center for Postmarket Evaluation and Research for Drugs and Biologics, and the Director of the Center for Devices and Radiological Health, to submit to Congress a report that identifies gaps in the current process of postmarket surveillance of devices approved under the Federal Food, Drug, and Cosmetic Act, includes recommendations on ways to improve gaps in postmarket surveillance of devices, and identifies the changes in authority needed to make those improvements.

Table 1. Comparison of Proposals for Clinical Trials Reporting and Publication in the 110th Congress

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
Title	Data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions	FACT Act	Food and Drug Administration Revitalization Act	Food and Drug Administration Revitalization Act	Enhancing Drug Safety and Innovation Act of 2007	Food and Drug Administration Safety Act of 2007
Sponsor		Senator Dodd	Senator Kennedy	Senator Enzi	Representative Waxman	Senator Grassley, Representative Tierney
Law Amended	(Existing law) PHSA (42 U.S.C. § 282 (j))	PHSA (42 U.S.C. 282), as amended by Public Law 109-482; and Section 492 A(a) of the PHSA	PHSA (42 U.S.C. 282), as amended; and Section 492 A(a) of the PHSA	Subsection (i) of section 402 of PHSA (42 USC 282 as amended by PL 109-482).	Subsection (i) of section 402 of PHSA (42 USC 282), as amended by PL 109-482.	Chapter V of the FFDCA (21 USC 351, et seq.)
Registry and/or Results Database Required	Registry only (clinicaltrials.gov); with sponsor consent, registry may also include information about the results of	Both	Registry expanded, and includes links to certain results. Results database to be created by	Both	Both	Both, to the extent that information to be made public is about ongoing studies and their results.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
	registered trials, including potential toxicities or adverse effects		HHS Secretary rulemaking following recommendations to be made in NIH Director's report about best, validated method of making trial results publically available.			
Product Trial Types Included	**REGISTRY:** Drugs	**BOTH:** Drugs, biologics, devices. Information about other trials may be voluntarily submitted.	**REGISTRY:** Drugs, devices, biologics	**BOTH:** Drugs, biologics, eventually possibly devices	**BOTH:** Drugs, devices, biologics	**BOTH:** Drugs and biologics.
Public Access	**REGISTRY:** Yes, via information systems, which are to include toll-free telephone communications	**BOTH:** Yes, via information systems, which are to include toll-free telephone	**REGISTRY:** Yes, via Internet. Internet posting and FOIA request disclosures limited to terms of the act.	**BOTH:** Yes, via Internet. Internet posting and FOIA request disclosures limited to terms of the act.	**BOTH:** Yes, via Internet. FOIA request disclosures not available for results for which	**BOTH:** Yes, via publication in the Federal Register and posting on an Internet website.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		communications. Provisions related to disclosure of FDA reviews supersede FOIA.	Secretary promulgates regulations that notice of posting be part of informed consent.	Secretary promulgates regulations that notice of posting be part of informed consent.	the principal investigator is seeking publication.	
Location of Databases	**REGISTRY:** NLM at NIH is current location	**BOTH:** Not specified, but bill amends the portion of the USC related to the current registry, which is located at NLM at NIH.	**REGISTRY:** NLM at NIH	**BOTH:** NIH. **REGISTRY:** Either supplants or builds on clinicaltrials.gov, whichever is more efficient.	**BOTH:** NIH. **REGISTRY:** Either supplants or builds on clinicaltrials.gov, whichever is more efficient.	Not specified.
Links Between Registry, Results Database	**REGISTRY:** Not specified; except that the activities of the data bank are to be integrated and coordinated with related activities of other agencies of the DHHS, and, to the extent practicable,	Not specified, except that the Secretary shall assign each clinical trial a unique identifier to be included in the registry and in the database.	**REGISTRY:** Entries link to certain existing results.	**REGISTRY:** Entries link to results entries.	**BOTH:** Corresponding registry and results database entries link to one another.	None specified.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
	coordinated with other data banks containing similar information.					
Who Submits Information	**REGISTRY:** Sponsor	**BOTH:** Responsible party (RP): if such clinical trial is the subject of an investigational new drug application or an application for an investigational device exemption — the sponsor; if not — the person that provides the largest share of monetary support, but if that person is federal or state agency — the principal investigator; if the main funder is a nonprofit — the	**REGISTRY:** Responsible party (RP): sponsor; if no sponsor exists-grantee, contractor or awardee of federal funding; if designated by sponsor, grantee, contractor or awardee - principal investigator.	**BOTH:** Responsible party (RP): sponsor, or principal investigator if designated by sponsor	**BOTH:** Responsible party (RP): primary sponsor as defined by WHO, or principal investigator (PI) if designated by sponsor and if PI is responsible for conducting the trial, has access to and control over data, has the right to publish trial results, and has the responsibility to meet the RP responsibilities.	**BOTH:** Sponsor

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		nonprofit alone or jointly with the principal investigator; if a request is made to the Secretary that another person be the RP, and that person provides monetary support for the trial is responsible for the conduct of the trial and will be responsible for submitting required trial information — that person.				

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
Who Receives Information	**REGISTRY:** HHS Secretary, acting through the NIH Director	**BOTH:** HHS Secretary, acting through the NIH Director	**REGISTRY:** Director of NIH	**BOTH:** Director of NIH	**BOTH:** Director of NIH	**BOTH:** Director of FDA Center for Postmarket Evaluation and Research for Drugs and Biologics created by Act (Center Director)
Timing of Submission	**REGISTRY:** Not later than 21 days after the approval of the protocol	**REGISTRY:** **-Initially:** not later than 21 days after the trial is opened for enrollment. **RESULTS:** **-Initially:** implied same date as for registry. (To the extent practicable, the Secretary ensures that where the same information is required for the registry and the database (such as	**REGISTRY:** **-Initially:** not later than 21 days after the first patient is enrolled. **-Change in enrollment status:** not later than 30 days after change. **-Completion of trial:** not later than 30 days after the last patient enrolled in the clinical trial has completed his or her last medical	**REGISTRY:** **-Initially:** not later than14 days after first patient is enrolled **-Change in Enrollment Status:** not later than 30 days after change **-Final Submission:** Not later than 30 days after last enrolled patient has last medical visit **RESULTS:** **-Generally:** Not	**REGISTRY:** **-Initially:** not later than14 days after first patient is enrolled **-Updates:** not less than once every 6 months **-Change in Enrollment Status:** not later than 30 days after change **-Notice of trial completion:** Not later than 30 days after final collection of data	**BOTH:** **-During the study:** not less frequently than every 90 days **-Upon Study Completion:** results to be submitted upon completion of study. Completion date determined by Center Director.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		initial information required for the database), a process exists to allow the RP to make only one submission. **-Results:** not later than 1 year than the earlier of the trials' estimated or actual completion date (extensions possible). **BOTH:** **-Changes**: within 30 days of the date on which the RP or principal investigator became aware of the change	visit, whether the clinical trial conducted according to the prespecified protocol or plan was terminated (extensions possible).	later than 1 year after last enrolled patient has last medical visit (extensions possible). **-Changes in regulatory status:** within 30 days after change	from subjects for primary and secondary outcomes **RESULTS:** **-Generally:** Not later than 1 year after earlier of estimated or actual completion date (extensions possible) **-Updates:** every 6 months for 10 years from when initial posting was required **-Changes in regulatory status:** within 30 days after change	
Timing of Posting	**REGISTRY:** Not specified	**BOTH:** In making information about clinical trials publicly available, the Secretary shall	**REGISTRY:** **-Trials of drugs and biological products:** within 30 days of submission	**REGISTRY:** **-Not specified** (NIH Director ensures the registry information is	**REGISTRY:** **-Not specified** (NIH Director ensures the registry information is	**BOTH:** Not less often than every 90 days.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		make information available as soon as practicable after receiving the data, and shall seek to be as timely and transparent as possible. (Postponement and extensions for publication are possible).	**-Trials of devices:** within 30 days of clearance under section 510(k) of the FFDCA or approval under sections 515 or 520(m) of the FFDCA **-Links to trial results (from FDA and NIH information) that form the basis of an efficacy claim or are conducted after the drug or biologic is approved or the device is cleared or approved:** not earlier than 30 days after the date of approval or clearance, not later than 30 days after the produce becomes	made publically available via Internet) **RESULTS:** (*delays of up to 2 years possible if seeking publication*) **-Pre-approval studies:** not later than 30 days after approval or issuance of not approvable letter **-Post-approval studies generally:** not later than 30 days after submission **-Post-approval studies of new uses in which the manufacturer is a trial sponsor and certifies it is seeking or will seek approval within 1 year:** not later than 30 days	made publically available via Internet) **RESULTS:** (*delays of up to 2 years possible if seeking publication*) **-Pre-approval studies**: not later than 30 days after approval or issuance of not approvable letter **-Summaries of medical, clinical pharmacology reviews of pre-approval and new use studies:** within 90 days of applicable date **-Post-approval studies generally**: within 30 days of submission **-Post-approval studies of new uses in which**	

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
			publically available.	after approval, issuance of not approvable letter, or application withdrawal, or 2 years after certification.	**manufacturer is a trial sponsor and certifies it is seeking or will seek approval within 1 year:** not later than 30 days after approval, issuance of not approvable letter, or application withdrawal; or 2 years after certification.	
Searchable By	**REGISTRY:** Not specified (But for a list of required data elements, see that entry below.)	**BOTH:** Not specified (But for a list of required data elements, see that entry below.)	**REGISTRY:** -Indication, using Medical Subject Headers -Source of support -Study phase -Treatment -Recruitment status -Age group (including pediatric subpopulations) -Study location	**REGISTRY:** -Enrollment status -Approval status **RESULTS:** -Each financial sponsor -Clinical trial phase -Safety issue -Drug name **BOTH:** -Indication, using Medical Subject Headers	**REGISTRY:** -Trial enrollment status -Trial sponsor **RESULTS:** -Status of FDA application -Trial phase -Product name -Each financial sponsor **BOTH:** -Indication, using Medical Subject	**BOTH:** Not specified. (But for a list of required data elements, see that entry below.)

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
			-National Clinical Trial number or other identification number	-Sponsor	Headers -Safety issue being studied -Trial sponsor	
Trials Included	**REGISTRY:** **-Investigational new drug trials:** trials (whether federally or privately funded) of experimental treatments for serious or life- threatening diseases and conditions under regulations promulgated pursuant to section 21 USC 355(i) [re investigational new drugs]. **-Treatment use of investigational new drugs:** information pertaining to experimental treatments for serious or life-threatening diseases and conditions	**REGISTRY:** **- Non-phase I clinical trials of drugs, devices, biologics:** trials testing a treatment for a life-threatening disease or condition, that are federally funded, used in requesting FDA approval, and/or conducted in the United States. **RESULTS:** **- Non-phase I Drug, device, or biologic clinical trials, and those required by the HHS Secretary in**	**REGISTRY:** **-Device trials:** prospective study of health outcomes comparing an intervention against a control in human subjects intended to support an application under section 520 (m) [re humanitarian devices] or 515 [re premarket approval of devices] or a report under section 510(k) [re device clearance] of the FFDCA; pediatric	**REGISTRY:** **-Premarket:** Trials to verify efficacy and establish doses **-Confirmatory:** All **RESULTS:** **-Premarket:** Trials to verify efficacy and establish doses if recommended by a required GAO study and required by the HHS Secretary through rulemaking; fast track product trials if used as the basis for efficacy. **-Confirmatory:** Premarket	**BOTH:** **-Drug, device, biologic clinical trials:** Trials testing a products' safety or effectiveness if conducted in the U.S. or if the product has FDA approval or is the subject of an application for FDA approval.	**BOTH:** **-Preapproval:** Studies required by the Center Director of drugs and biologics being considered for FDA approval under FFDCA section 505 or PHSA Section 351 [reapproval of drugs and biologics] **-Postmarket:** Studies required by the Center Director of drugs approved by FDA under FFDCA section 505, or biologics licensed by FDA under

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
	that may be available - (i) under a treatment investigational new drug application that has been submitted to the Secretary under 21 USC 360bbb(c); or (ii) as a Group C cancer drug (as defined by the National Cancer Institute).	**the interest of public health:** if federally funded, used in requesting FDA approval, and/or conducted in the United States. **BOTH:** clinical trial means a research study in human volunteers to answer specific health questions, including treatment, prevention, diagnostic, screening, and quality-of-life trials	postmarket surveillance as required under section 522 of the FFDCA (as amended by the bill). **-Drug and biologic trials:** a controlled clinical investigation of a product subject to section 505 [re drug approval] or 351 [re approval of biological products] of the FFDCA. **-Other trials:** voluntary submissions may be made.	confirmatory trials **BOTH:** **-Postmarket:** all. **-Pediatric Pharmacokinetic:** all		FFDCA section 351.
Exceptions (trials not included)	**REGISTRY:** Information relating to an investigation if the sponsor has provided a detailed certification to the Secretary that disclosure would	**BOTH:** **-Phase I clinical trials** conducted solely to test the safety of an unapproved drug or unlicensed	**REGISTRY:** **-Device trials:** limited studies to gather essential information used to refine the device or design a	**BOTH:** **-Exploratory** trials solely to assess safety, evaluate pharmacokinetics, or verify efficacy	**BOTH:** **-Pharmacokinetic and toxicity studies:** a clinical trial to determine the safety of a use of a drug that is	None.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
	substantially interfere with the timely enrollment of subjects in the investigation, unless the Secretary, after the receipt of the certification, provides the sponsor with a detailed written determination that such disclosure would not substantially interfere with such enrollment.	biological product, pilot or feasibility studies conducted to confirm the design and operating specifications of an unapproved or not yet cleared medical device may be included with RP consent. **-Clinical trials of other health-related interventions** may be included with consent of RP.	pivotal trial and that is not intended to determine safety and effectiveness of a device. **-Drug and Biologic Trials:** Phase I trials.	**-Observational** studies	designed solely to detect major toxicities in the drug or to investigate pharmacokinetics, unless the clinical trial is designed to investigate pharmacokinetics in a special population or populations; and **-Feasibility studies:** a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary focus is feasibility.	
Registry Data Elements	-Purpose of each experimental drug -Eligibility criteria -Location of trial sites -Point of contact for enrollment	-Trial title -Unique identifier -Trial description -Trial phase -Trial type -Trial purpose	-WHO elements (See **Appendix A**.) -City, state, zip code of study -Toll free number	-Sponsor -Trial purpose -Patient population description -General	-WHO elements (See **Appendix A**.) -City, state, zip code of study -Estimated	-Type of study -Nature of study -Primary and secondary outcomes -Date the Center

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
	-Description of whether and how the manufacturer or sponsor will respond to requests for protocol exception, with appropriate safeguards, for single- patient and expanded protocol use of the new drug, particularly in children -With sponsor consent, may include information about the results of included trials, including potential toxicities or adverse effects	-Primary, secondary outcome measures -Date outcome measures will be assessed -Dates and details of revisions to outcomes -Eligibility and exclusion criteria -Whether and how requests for single-patient and expanded protocol use (particularly in children) will be addressed -Trial and enrollment status at individual sites -Estimated completion date -Trial location -RP identity and contact information -Sponsor -Funding source -Experimental	for study -Whether there is expanded access for unapproved drugs and biologics under FFDCA section 561 [re emergency situations, patient access to treatments for serious diseases, treatment uses] -Other data elements as appropriate -Links to results from certain FDA submissions, NIH information (Medline cites and NLM database of product labels), and previously existing databank entries	description of results, trial design changes, and reasons for changes -WHO elements (See **Appendix A**.) -City, state, zip code of study -Whether compassionate use is available -Elements specified by Secretary	completion date -RP identity and contact information -Whether there is expanded access for unapproved drugs and biologics under FFDCA section 561 [re emergency situations, patient access to treatments for serious diseases, treatment uses] -Restrictions on non-employees' discussion or publication of results -Elements specified by Secretary	Director required the study or that the sponsor agreed to the study -Deadline for study completion -If deadline not met, explanation of why not -Study progress reports -Center Director determinations (with reasons, references, supporting materials) about whether the product presents an unreasonable public risk, and required corrective action

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		treatments for serious or life-threatening conditions available under a treatment investigational new drug application or as a Group C cancer drug.				
Results Data Elements	None.	-Title -Unique identifier -Product tested -Trial description in lay language -Trial phase, type -Trial purpose -Demographic data -Estimated completion date -Study sponsor and funding source -Primary, secondary outcome measures -Date outcome	None.	-Indication studied -Safety issue -Status of FDA application -Trial phase **TECHNICAL REPORT:** -Each sponsor -Scientific point of contact -Description of patient population -Summary of aggregate data assessing primary and secondary endpoints, safety information	-Indication studied -Safety issue -Status of FDA application -Trial phase **TECHNICAL REPORT:** -Each sponsor -Scientific point of contact -Description of patient population -Summary of aggregate data assessing primary and secondary endpoints, safety information	-Type of study -Nature of study -Primary and secondary outcomes -Date the Center Director required the study or that the sponsor agreed to the study -Deadline for study completion -If deadline not met, explanation of why not -Study progress reports -Center Director

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		measures assessed -Dates, details of outcome revisions -Actual completion date, reason for difference from estimate -If terminated, reason for termination -Results summary with trial design, methodology, outcome measures, summary data tables, statistical significance of results -Safety data, including adverse event information -Peer-reviewed publications -Description of results review process, protocol -Status of FDA application or		-Information about subjects quit trial -Restrictions on non-employees' discussion or publication of results. -Link to peer reviewed publications -completion date -FDA adverse regulatory action **NONTECHNI-CAL REPORT:** -Point of contact -General description of results, trial design changes, and reasons for changes **BOTH REPORTS:** -Trial purpose -Trial sponsor -General description of results, trial design changes, and	-Information about subjects quit trial -Restrictions on non-employees' discussion or publication of results. -Link to peer reviewed publications -completion date -FDA adverse regulatory action **NONTECHNI-CAL REPORT:** -Point of contact -General description of results, trial design changes, and reasons for changes **BOTH REPORTS:** -Trial purpose -Trial sponsor -General description of results, trial design changes, and	determinations (with reasons, references, supporting materials) about whether the product presents an unreasonable public risk, and required corrective action

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		reason trial not submitted to FDA		reasons for changes	reasons for changes	
Enforcement and Corrections	**REGISTRY:** None specified. General mechanisms for enforcing compliance with FDA requirements may be applicable, but have not been applied by FDA.	**BOTH:** -Sponsors of FDA new drug applications submit to Secretary certification of compliance with FFDCA. If not, after hearing, Secretary imposes $10,000/day civil monetary penalty until certification submitted. If information is inaccurate and sponsor knew or should have known, after notice and hearing, Secretary orders sponsor to pay civil monetary penalty of $100,000 to $2,000,000 for any	**REGISTRY:** -RP ensures submissions not false or misleading. -No federal agency may release research grant funds to noncompliant RPs. -For applicable trials funded by FDA, NIH, AHRQ, or VA, progress report forms include certification of compliance. Agency heads verify compliance before releasing grant funds to RPs. Secretary consults with other federal agencies to determine whether	**BOTH:** -RP ensures submissions not false or misleading. -No federal agency may release grant funds to noncompliant RPs. -FDA Commissioner verifies required submissions were made when considering applications for investigational drug exemptions, new drug approvals, biologics licences. After notice to RP, opportunity to correct, Secretary refuses to file application.	**BOTH:** -RP ensures submissions not false or misleading. -No federal agency may release research grant funds to noncompliant RPs. -For applicable trials funded by FDA, NIH, AHRQ, or VA, progress report forms include certification of compliance. Agency heads verify compliance before releasing grant funds to RPs. Secretary consults with other federal agencies to determine whether	**BOTH:** -A product is considered misbranded if a sponsor fails to comply with an order or requirement of the act. -Other penalties are created for failure to conduct required studies.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		30-day period. -To be eligible for a federal grant, contract, or cooperative agreement, principal investigator certifies Act compliance. Noncompliance, after notice, leads to ineligibility, posting of noncompliance notice in database. -In trial with nonfederal support, Act noncompliance leads to notice, opportunity to correct, hearing, $10,000/day penalty until compliant.	studies funded by them and conducted under 45 CFR 46 [re federal protections for human subjects] merit similar procedures. -Applications or submissions under FFDCA sections 505, 515, 520(m), 351, or 510(k) [re new drugs, biologics and devices], must have certifications of compliance. -Secretary may impose FFDCA penalties for noncompliance.	-Secretary checks registry to ensure corresponding results are filed. After notice to RP, opportunity to correct, Secretary reports noncompliance to federal agencies and Office of Human Research Protections, posts notice of noncompliance in registry and database. -Secretary ensures content is not false or misleading and non-promotional by checking a representative sample. After notice to RP, opportunity to correct, Secretary may impose FFDCA penalties	studies funded by them and conducted under 45 CFR 46 [re federal protections for human subjects] merit similar procedures. -NIH Director checks registry to ensure corresponding results are filed. After notice to RP, opportunity to correct, Director reports noncompliance to federal agencies and Office of Human Research Protections, posts notice of noncompliance in registry and database. -Applications or submissions under FFDCA sections	

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
					505, 515, 351, or 510(k) [re new drugs, biologics and devices], must have certifications of compliance. -Secretary may impose FFDCA penalties for noncompliance, including civil monetary penalties ($10,000/day for first violation, $20,000/day for each subsequent violation) created by Act.	
Required Studies or Reports	None.	**BOTH:** Not later than 1 year after enactment, Secretary submits to appropriate committees of Congress a report on the status of the implementation of Act requirements	**RESULTS:** The NIH Director conducts a study to determine the best, validated methods of making trial results public after the approval of a drug that is the subject of an	**RESULTS:** Not earlier than 2 years after results database established, Comptroller General initiates a GAO study of inclusion of certain premarket trials: burden to	None required by clinical trials title.	HHS Secretary required to report to Congress on device postmarket safety within 6 months of enactment.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
		including number and types of trials submitted. **REGISTRY:** Secretary contracts with IOM to conduct a study of the extent to which data submitted to the registry and database have impacted the public health. Not later than 6 months after the contract date, IOM submits study to Secretary	applicable drug trial. Director submits findings to the HHS Secretary within 18 months of initiating the study.	sponsors and agencies, benefit to patients and health providers, recommendations. Makes report to HELP, Energy and Commerce.		
Authorized Appropriations	**REGISTRY:** Such sums as may be necessary; Fees collected under section 21 USC 379h [re FDA prescription drug user fees] may not be used for the registry.	**BOTH:** Such sums as may be necessary	**BOTH:** $10,000,000 each FY	**BOTH:** $10,000,000 each FY	**BOTH:** $10,000,000 each FY	**For entire Act:** FY2008: $50,000,000 FY2009: $75,000,000 FY2010: $100,000,000 FY2011: $125,000,000 FY2012: $150,000,000

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
Preemption	None.	None.	**BOTH:** Yes. No state or political subdivision of a state may require or effect registration of trials or results.	**BOTH:** Yes. No state or political subdivision of a state may require or effect registration of trials or results.	**BOTH:** Yes. No state or political subdivision of a state may require or effect registration of trials or results.	None.
Safe Harbor	None.	None.	**BOTH:** Somewhat. Compliant submissions shall not be considered (1) by Secretary as evidence of a new intended use different from labeling, or (2) as FFDCA labeling, adulteration, or misbranding.	**BOTH:** Somewhat. Compliant submissions shall not be considered (1) by Secretary as evidence of a new intended use different from labeling, or (2) as FFDCA labeling, adulteration, or misbranding.	**BOTH:** Somewhat. Compliant submissions shall not be considered (1) by Secretary as evidence of a new intended use different from labeling, or (2) as FFDCA labeling, adulteration, or misbranding.	None.
Effective Dates	**REGISTRY:** Currently operational	Not specified.	**REGISTRY:** -Generally: October 1, 2007 -Regulations become effective 90 days after issuance of HHS Secretary's	**BOTH:** Databases to be established not later than 1 year after enactment.	**BOTH:** -Databases established not later than 1 year after enactment.	Not specified.

	Current Law	S. 467	S. 1082	S. 484	H.R. 1561	S. 468 / H.R. 788
			issuance of final rule. (Final rule issued pursuant to Act to be issued not later than 18 months after Act's enactment, and after notice and comment.) -Funding restrictions take effect 210 days after regulations' effective date.			

Appendix A. World Health Organization, International Clinical Trials Registry Platform, Registration Data Set (Version 1.0)

ITEM	DEFINITION / EXPLANATION
Primary Register and Trial ID #	Name of Primary Register, and the unique ID number assigned by the Primary Register to this trial.
Date of Registration in Primary Register	Date when trial was officially registered in the Primary Register YYYY/MM/DD.
Secondary ID#s	Other identifying numbers and issuing authorities besides the Primary Register, if any. Include the sponsor name and sponsor-issued trial number (e.g., protocol number) if available. Also include other trial registers that have issued an ID number to this trial. There is no limit on the number of Secondary ID numbers that can be provided.
Source(s) of Monetary or Material Support	Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company).
Primary Sponsor	The individual, organization, group or other legal person taking responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the study design meets appropriate standards and to ensure appropriate conduct and reporting). In commercial trials, the primary sponsor is normally the main applicant for regulatory authorization to begin the study. It may or may not be the main funder.
Secondary Sponsor(s)	Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship. A secondary sponsor may have agreed -to take on all the responsibilities of sponsorship jointly with the primary sponsor; or -to form a group with the primary sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or -to act as the sponsor's legal representative in relation to some or all of the trial sites; or -to take responsibility for the accuracy of trial registration information submitted.
Contact for Public Queries	Email address, telephone number, or postal address of the contact who will respond to general queries, including information about current recruitment status
Contact for Scientific Queries	Email address, telephone number, or postal address, and affiliation of the person to contact for scientific queries about the trial (e.g., principal investigator, medical director employed by the sponsor). For a multi-center study, enter the contact information for the lead Principal Investigator or overall scientific director.
Public Title	Email address, telephone number, or postal address, and affiliation of the person to contact for scientific queries about the trial (e.g., principal investigator, medical director employed by the sponsor). For a multi-center study, enter the contact information for the lead Principal Investigator or overall scientific director.

Scientific Title	Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available.
Countries of Recruitment	The countries from which participants will be, are intended to be, or have been recruited.
Health Condition(s) or Problem(s) Studied	Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error). If the study is conducted on healthy human volunteers belonging to the target population of the intervention (e.g., preventative or screening interventions), enter the particular health condition(s) or problem(s) being prevented. If the study is conducted using healthy human volunteers not belonging to the target population (e.g., a preliminary safety study), an appropriate keyword will be defined for users to select.
Intervention(s)	Enter the specific name of the intervention(s) and the comparator/control(s) being studied. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., “low-fat diet, exercise”). The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter “placebo” or “no treatment” as applicable. For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc).
Key Inclusion and Exclusion Criteria	Inclusion and exclusion criteria for participant selection, including age and sex.
Study Type	A single arm study is one in which all participants are given the same intervention. Trials in which participants are assigned to receive one of two or more interventions are NOT single arm studies. Crossover trials are NOT single arm studies. A trial is “randomized” if participants are assigned to intervention groups using a method based on chance (e.g., random number table, random computer-generated sequence, minimization, adaptive randomization).
Date of First Enrollment	Anticipated or actual date of enrollment of the first participant (YYYY/MM).
Target Sample Size	Number of participants that this trial plans to enroll.
Recruitment Status	Recruitment status of this trial. -Pending: participants are not yet being recruited or enrolled at any site -Active: participants are currently being recruited and enrolled -Temporary halt: there is a temporary halt in recruitment and enrollment -Closed: participants are no longer being recruited or enrolled
Primary Outcome(s)	Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effects of the int[ervention(s). Enter the names of all primary outcomes in the trial as well as the pre-specified timepoint(s) of primary interest. Be as specific as possible with the metric used (e.g., “% with Beck Depression Score > 10" rather than just “depression”). Examples: Outcome Name: all-cause mortality, Timepoints: 5 years; or Outcome Name: Mean Beck Depression Score, Timepoint: 18 weeks

Secondary Outcome(s)	Secondary outcomes are events, variables, or experiences that are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: all-cause mortality at 1 year, 3 years), or may involve a different event, variable, or experience altogether (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: hospitalization rate at 5 years). Enter the name and timepoint(s) for all secondary outcomes of clinical and/or scientific importance. Be as specific as possible with the metric used (e.g., "% with Beck Depression Score > 10" rather than just "depression"). Examples: Outcome Name: all-cause mortality, Timepoints: 6 months, 1 year; or Outcome Name: Mean glycosylated hemoglobin A1C, Timepoints: 4 and 8 weeks

Source: WHO, ICTRP, "Registration Data Set (version 1.0)," (March 16, 2007), at [http://www.who.int/ictrp/data_set/en/index1.html], visited Apr. 16, 2007.