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Compliance date: The compliance date of this final rule is March 7, 2012, for clinical trials that are initiated on or after the compliance date. See section III of this document for an additional explanation of the compliance date and required implementation of this final rule.

FOR FURTHER INFORMATION CONTACT: Jarilyn Dupont, Office of Policy, Office of Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, rm. 4248, Silver Spring, MD 20993–0002, 301–796–4830.

SUPPLEMENTARY INFORMATION:

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I. Introduction

In the **Federal Register** of December 29, 2009 (74 FR 68750), FDA issued a notice of proposed rulemaking (NPRM) to amend 21 CFR 50.25, its regulations governing informed consent documents and processes. This final rule revises the current informed consent regulations to require a new element for informed consent documents and processes that will inform the potential clinical trial participant that information about applicable clinical trials has been, or will be, entered into a databank that is publicly accessible at *http://www.ClinicalTrials.gov*. (*See* section IV.F of this document for a discussion of applicable clinical trials.) The final rule adds this requirement in a new paragraph, § 50.25(c), and redesignates existing paragraphs.

This final rule is issued under section 801 of FDAAA (Pub. L. 110–85, September 27, 2007), which requires that information on an applicable clinical trial be submitted to NIH for inclusion in the clinical trial registry databank. This section also requires that the Secretary of the Department of Health and Human Services (HHS) update certain informed consent regulations to mandate that informed consent documents and processes include a statement that the required clinical trial information has been or will be submitted for inclusion in the registry databank. The current informed consent regulations do not include provisions similar to those required by FDAAA. (*See* parts 50 and 312 (21 CFR parts 50 and 312) and 21 CFR 812.2(b)(1)(iii) and 812.25(g)).

Section 801 of FDAAA amends the Public Health Service Act (the PHS Act) to require the Secretary, acting through the Director of NIH, to expand the existing clinical trial registry databank established under section 113 of the Food and Drug Administration Modernization Act (FDAMA), enacted November 21, 1997 (Pub. L. 105–115 currently codified at 42 U.S.C. 282(i)). The new provision requires the Director to ensure that the databank is made publicly available through the Internet and to expand the databank to require the submission of specified information for applicable drug clinical trials and applicable device clinical trials. (The term "drug" includes biological products regulated under section 351 of the PHS Act (42 U.S.C. 262).) The provision also requires the Secretary of HHS to ensure that the databank includes links to results information for those clinical trials that form the primary basis of an efficacy claim or are conducted after the drug involved or device involved is cleared or approved. In addition, section 801(b)(3)(A) of FDAAA states:

> NEW DRUGS AND DEVICES.—
> INVESTIGATIONAL NEW DRUGS.—Section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) is amended in paragraph (4), by adding at the end the following: "The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 402 of the Public Health Service Act."

II. Overview of the Final Rule

We considered all of the comments to the NPRM and the additional data and accompanying materials submitted with the comments. We also consulted with our internal experts on informed consent documents and processes as well as our internal experts in communicating health-related information to the public, clinical trial participants, and patients in evaluating the required statement.

In response to the comments, and based on our internal reconsideration of the proposed requirements in the NPRM, we have amended the specific language of the statement required to be included in informed consent documents and processes. The mandatory statement is now shorter, less complex, and more understandable for potential clinical trial participants. Specific terms that are not commonly used by lay persons, or were deemed to be misleading or confusing, have been clarified and simplified. The mandatory statement has been revised to facilitate understanding while maintaining the purpose of the statutory provision.

In response to comments expressing confusion and/or concern over the proposed placement of the new requirement as a "basic" element of informed consent under § 50.25(a), a new paragraph (c) has been added and the existing paragraphs have been redesignated. This separate new paragraph emphasizes the unique basis of the new element—required only for applicable clinical trials—as compared with existing basic elements which align with various ethics codes and apply to all clinical investigations regulated by FDA and clinical investigations that support applications for research or marketing permits for products regulated by FDA.

New paragraph § 50.25(c) interacts with all other requirements of part 50 as do the other requirements and provisions of § 50.25. Similar to other informed consent elements, it is subject to the regulations governing documentation of informed consent (§ 50.27) and Institutional Review Board (IRB) waivers (§ 56.109(c)(1) (21 CFR 56.109)). When a short form written consent document is chosen (§ 50.27(b)(2)), a short form and written summary must be provided to the clinical trial participant. All of these are considered "informed consent documents" and must contain the new statement (Ref. 1). For example, if an IRB waives the requirement for a signed written consent form under § 56.109(c)(1), and requires "the investigator to provide subjects with a written statement regarding the research," this written statement is considered a part of the documentation of ensuring the informed consent of the participant and thus, it must include the new statement (§ 56.109(d)).

III. Compliance Date

In response to comments, and after consideration of the intent and purpose of the new statutory requirement, we have determined that the compliance date of new § 50.25(c) will be 1 year after the effective date of this final rule for all informed consent documents and processes related to a clinical investigation that is initiated on or after the compliance date of this rule. In section IV.B of this document we provide, in our responses to the comments made concerning the effective date, additional explanation of the application of the compliance date to particular clinical investigations.

IV. Comments on the Proposed Rule

We received 68 comments on the NPRM. Comments were received from IRBs, academic research centers, clinical investigators, physicians, health care professional societies, trade organizations representing clinical research organizations, drug and device sponsors, blood banks, clinical research organizations, research hospitals, medical device manufacturers, nonprofit organizations for ethical research, patient advocacy organizations, health care attorneys, pharmacy and law students, and others.

To make it easier to identify comments and our responses, the word "Comment," in parentheses, will appear before each comment, and the word "Response," in parentheses, will appear before each response. We also have numbered the comments to make it easier to distinguish between comments; the numbers are for organizational purposes only and do not reflect the order in which we received the comments or any value associated with the comment. We have combined similar comments under one numbered comment.

A. General Comments

(Comment 1) We received comments that objected to adding any statement to informed consent documents about submitting information to the databank

after NIH issued regulations to implement changes to *ClinicalTrials.gov*. This comment recommended that FDA issue a guidance instead of a regulation because a guidance would be easier to change, if necessary, after the NIH regulations issued.

(Response) We decline to issue a guidance in lieu of a regulation. Section 801(b)(3)(A) of FDAAA makes clear that the "Secretary shall update [FDA's] regulations," not merely issue a guidance. NIH's subsequent regulations will not impact the specific language of the new element as the language of the required statement is not affected by the statutory or regulatory interpretation of an "applicable clinical trial." There is a statutory definition of "applicable clinical trial" and no matter what additional regulatory explanation of "applicable clinical trial" is provided in a future rulemaking, it will not affect or change the required statement. Changes to the definition only will impact the determination made by sponsors and investigators about their clinical trial and whether it is an "applicable clinical trial" subject to the registration requirements of 42 U.S.C. 282(j)(1)(A), section 402(j)(1)(A) of the PHS Act. That separate determination is made prior to the inclusion of the mandatory statement in informed consent documents and processes.

C. New Section 50.25(c)

In order to address some of the concerns raised by comments, and on our own initiative, we have created a new paragraph (c) in § 50.25 to include the requirements of this final rule. While this is a "required" element of informed consent documents and processes, it is only required if the clinical trial is an "applicable clinical trial" as defined in FDAAA, 42 U.S.C. 282(j)(1)(A), section 402(j)(1)(A) of the PHS Act, and any relevant regulation. Although there were comments suggesting that § 50.25(b) was the more appropriate location for the required provision, we are concerned that such placement would be confusing given the specific requirement of section 801(b)(3)(A) of FDAAA and the mandatory nature of its inclusion when an applicable clinical trial is involved. To avoid any confusion, we have created a new paragraph (c) in § 50.25 and redesignated existing paragraphs.

(Comment 7) Many comments suggested that the rule should amend § 50.25(b), "Additional Elements of Informed Consent," rather than § 50.25(a), "Basic Elements of Informed Consent." Some comments reasoned that the new statement could not be considered a "basic element" because it would not apply to all clinical trials, only applicable clinical trials. For example, a phase 1 or device feasibility study would not be considered an applicable clinical trial under the statutory definition in FDAAA. These comments further reasoned that the new statement qualified as an "additional element" because it would be required only "when appropriate" (i.e., in applicable clinical trials).

(Response) We agree with the comments that the element should not be included in § 50.25(a) since the statutory provision limits it to inclusion in informed consent documents and processes only for "applicable clinical trials." We disagree, however, that the new statement should be included as an "additional element" under § 50.25(b) as this may raise further confusion as to the mandatory nature of the requirement.

As noted in the preamble to the final rule establishing the original informed consent elements, "[t]he elements listed as 'additional' are not material to every clinical investigation." (46 FR 8942 at 8949, comments 41 and 42) This new element, however, is statutorily required, and therefore, is material to *all* applicable clinical trials. Investigators do not have the discretion to determine whether the element is "appropriate" for a particular applicable clinical trial. Therefore, we decline to include the new element in § 50.25(b) and, instead, have created a new paragraph (c).

Nothing in this preamble affects our explanation in the 1981 final rule that "when any one of those additional elements would be appropriate, § 50.25(b) *requires* that the additional information be provided to the subject." (*emphasis added*)

(Comment 8) One comment recommended that FDA accomplish its statutory mandate to inform potential participants about the databank by amending § 50.25(a) to require a statement that describes whether results or other aspects of the trial may be published. This comment suggested that posting of results on *http://www.ClinicalTrials.gov* be trplicabwev:e wandate wehich pectfied that tnformed

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confusion in multinational clinical trials.

(Response) We agree and the revised statement indicates that the clinical trial description on *http://www.ClinicalTrials.gov* is required by "U.S. law."

F. Applicable Clinical Trials

(Comment 20) Several comments requested clarification on whether certain types of clinical trials, such as investigational device trials considered to be non-interventional, would be considered "applicable clinical trials." Several bloodbank organizations specifically inquired about clinical studies done by blood centers under investigational new drug applications (INDs) to validate new blood screening tests.

(Response) We decline to provide a more detailed definition of "applicable clinical trial," as it is not necessary for the purposes of this final rule. Section 801(a)(1) of FDAAA contains a statutory definition of this term (section 402(j)(1)(A) of the PHS Act). NIH/NLM also has elaborated on the meaning of "applicable clinical trial" at *http://prsinfo.clinicaltrials.gov/fdaaa.html* and at *http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf* (Ref. 14), which represents NIH's current thinking on the definitions. It is possible these definitions will be expanded upon in rulemaking by NIH. It is the responsibility of the sponsors and investigators to determine if their clinical trial meets the definition of an applicable clinical trial and to ensure compliance with the most current applicable statutory and regulatory requirements.

(Comment 21) Several comments recommended that the new statement not be required in the informed consent forms for clinical trials conducted outside of the United States, even if done in support of U.S. regulatory approval or conducted under an FDA IND. These comments stated that the new element should be required only when the clinical trials are conducted in the United States. These comments reasoned that: (1) Institutions and patients in other countries may object to or be offended by U.S.-centric language, (2) 21 other countries and regions already have in place or are in the process of implementing their own clinical trial registries, (3) foreign governments may prefer references to their own countries' registries, and (4) foreign IRBs and ethics committees may have their own informed consent requirements that conflict with the new statement.

(Response) We disagree. The new informed consent statement applies to all "applicable clinical trials" as defined in section 801(a)(1) of FDAAA. FDAAA does not limit "applicable clinical trials" to only those conducted in the United States; it also includes clinical trials that are not conducted in the United States that are subject to FDA's jurisdiction. Thus, informed consent documents and processes of all "applicable clinical trials," including those conducted in foreign countries, must include this new statement regarding the inclusion of information in the clinical trial databank. Congress did not provide an exemption from this requirement for applicable clinical trials conducted in foreign countries.

(Comment 22) One comment requested clarification on whether the new element is required only when a trial is conducted under a U.S. IND or is otherwise subject to FDA regulation at the time the research participant is enrolled. This comment focused in particular on data from non-U.S. trials that were not conducted under a U.S. IND or subject to FDA regulation at the time of inception but were later submitted in support of a new drug application (NDA).

(Response) Yes, the new requirement, § 50.25(c), applies only when a trial is conducted under a U.S. IND or is otherwise subject to FDA regulation.

(Comment 23) Several comments expressed concern that the new element would conflict with or cause confusion about other countries' registries or informed consent practices. One comment suggested that the new statement might conflict with the informed consent practices of IRBs and ethics committees residing outside the United States, and that foreign governments may not want references to
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should be noted for purposes of clarification that under 45 CFR 46.102(f) research using de-identified data would not be considered research on a human subject and, thus, the waiver of the informed consent requirement would not be applicable.

As a general matter, clinical research that both involves FDA-regulated products and is conducted or supported by HHS must meet the requirements of both sets of regulations. If such clinical trials are also applicable clinical trials under FDAAA, the new element must be included in the informed consent documents and process for these trials unless waived under part 50, regardless of whether an IRB determines that one or more of the elements is waiveable under 45 CFR part 46.

In some instances, review of records containing de-identified data may be exempt from IRB review because such record review does not qualify as human subject research. This is not always the case under FDA regulations and there are some circumstances in which the use of de-identified data requires IRB review. See §§ 56.101 and 56.103 and "Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff: Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable." (Ref. 15). The definition of an "applicable clinical trial," however, necessarily involves human subjects; thus an applicable clinical trial must comply with human subject regulations. The use of the new statement would not be implicated in research that does not qualify as human subject research under the definition of applicable clinical trial (Ref. 14).

It is also true that de-identified data (stripped of the 18 specified identifiers) fall outside of the Health Insurance Portability and Accountability Act of 1996 (Pub. L. 104–191) (HIPAA) privacy regulations and thus are not considered individually identifiable health information. As a consequence, clinical investigators need not obtain a subject's authorization to release de-identified data in a HIPAA authorization form, which is often included in a research consent form and accompanies an informed consent form. Regardless of whether an IRB determines that the information concerning submission of aggregate results to ClinicalTrials.gov does not need to be included in a HIPAA authorization form, the new element is still required by statute to be included in the informed consent documents and processes for applicable clinical trials.

(Comment 27) One comment suggested that the new element be included in an information sheet separate from the informed consent document, where the sheet explained the ClinicalTrials.gov Web site in simple terms.

(Response) FDAAA requires that the new element be included "in the informed consent documents and processes," not in an information sheet that is separate from an informed consent document. There is nothing in this final rule, however, that prevents an investigator, sponsor, or IRB from providing additional information in an information sheet further explaining ClinicalTrials.gov as part of the informed consent process.

(Comment 28) Many comments voiced a variety of opinions on the issue that no personally identifiable information is submitted to the databank or shown on the Web site. Several comments supported including such a statement to that effect in the required statement. Several comments requested that FDA include additional language in the new element to clarify any potential confidentiality issues posed by the databank. These comments suggested including: (1) Assurance that participants' names and identities will not be posted on ClinicalTrials.gov, will not be made available to employers, and will not be discoverable in court proceedings; (2) a statement that it is probable that participants' information will be re-identified; (3) a lay person description of data submitted to ClinicalTrials.gov and the Basic Element Results Definitions; and (4) an expanded description of the clinical trial registry and databank. Other comments recognized that no personal information about participants is submitted to ClinicalTrials.gov, so there are no privacy or confidentiality issues. Still another comment stated that its consent documents already contain language that non-identifiable information may be made public in scientific journals, presentations, and, if applicable, submitted to a government data bank/registry.

(Response) We have revised the new statement in the final rule so that it is clear that the Web site does not include information that can identify the clinical trial participant. We believe the new statement will provide reassurance to potential participants. The only results information submitted to the databank and posted on the Web site are aggregate statistics, such as those that typically appear in medical journals and product package inserts. No individual-level data are submitted to the databank. A review of the data fields on *http://www.ClinicalTrials.gov* for which data are required to be submitted by the sponsor/investigator confirms that there is no individual information, only aggregate, overall data (Ref. 16). Furthermore, § 50.25(a)(5) requires informed consent documents to explain the extent, if any, to which confidentiality of clinical trial data and the records of the clinical trial participant will be maintained. Nothing in this rule prohibits an investigator, sponsor, or IRB from including further explanation on the nature and confidentiality of information submitted to ClinicalTrials.gov in the informed consent form or process or a HIPAA authorization form.

(Comment 29) One comment suggested that the new statement should be inserted into the section of the consent document that invites the potential or enrolled participant to ask questions of the individual conducting the informed consent process. Such placement, according to the comment, would facilitate communication and encourage participants to ask questions.

(Response) The final rule does not require that the new statement be located in any particular section of the consent form. Investigators, sponsors, and IRBs have the flexibility to place the new statement in the consent form where they believe best serves participants' interests.

(Comment 30) One comment requested that the new statement include a phrase indicating that the information would be submitted to ClinicalTrials.gov "if required by law." The comment requested this change to eliminate the need for separate templates for studies that require registry in the databank and those that do not. Anticipated benefits were stated to be simplified documentation; reduced review time by sponsors, investigators, and IRBs; and reduced likelihood of using the incorrect consent template for a particular clinical study. Other comments apparently read the NPRM to require the statement in consent forms for all clinical trials and objected to the inclusion of the statement for trials that did not require registry in the databank.

(Response) We do not agree that it is necessary to include an additional phrase that would allow for a universal consent template. Sponsors and investigators already have to determine if a clinical trial is an applicable clinical trial in order to comply with the requirements of 42 U.S.C. 282(j), section 402(j) of the PHS Act. Adding the required statement to informed consent documents and processes will occur after that determination has been made

by the sponsor or investigator. Furthermore, because the mandatory statement requires specific language, it should not be burdensome for reviewers to determine whether the statement is included in the informed consent documents.

(Comment 31) Two comments expressed concern that the required new element would create an inconsistency between regulations governing applicable clinical trials of FDA-regulated products (part 50) and regulations governing clinical trials funded or supported by HHS (45 CFR part 46). The comments perceived the new element as contrary to FDA's objective to harmonize regulations of human-subject protection.

(Response) FDA does not agree that the required element would create an inconsistency or lack of harmony between the regulations on human subjects in the two sets of regulations. The new element merely entails an additional requirement for applicable clinical trials of FDA-regulated products in accordance with a statutory mandate, whether or not the trial is supported or funded by HHS. The new element does not conflict with any existing regulations under 45 CFR part 46.

(Comment 32) There were several comments that questioned the estimates contained in the preliminary Analysis of Impacts including the estimated time to explain the required statement if a potential participant asked questions.

(Response) These comments are addressed fully in section VII of this document.

V. Legal Authority and Enforcement

Section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(i)(4) requires drug manufacturers to "inform any human beings to whom [investigational] drugs * * * are being administered * * * that such drugs are being used for investigational purposes" and obtain consent prior to administering such drugs. Section 520(g)(3)(D) of the FD&C Act (21 U.S.C. 360j(g)(3)(D) contains a similar requirement for medical device manufacturers. Sections 505(i) and 520(g) of the FD&C Act also authorize the Secretary to issue regulations for the protection of human subjects in clinical investigations. Additionally, section 701(a) of the FD&C Act (21 U.S.C. 371(a)) confers general authority to the Secretary to issue regulations for the efficient enforcement of the FD&C Act.

Section 801(b)(3)A) of FDAAA amends section 505(i)(4) of the FD&C Act by adding at the end the following: "The Secretary shall update such regulations to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 402 of the Public Health Service Act." The regulations implementing section 505(i) of the FD&C Act can be found at parts 312 and 50. Part 312 sets forth regulations governing drug IND applications, while part 50 includes general requirements for human subject protection in all FDA-regulated clinical investigations and clinical investigations that support applications for research or marketing permits for products regulated by FDA, including trials for drugs and medical devices. Section 801(b)(3)(A) of FDAAA does not amend section 520(g) of the FD&C Act; however, in instances where the regulations have been amended to address human subject protection, FDA has not made distinctions between clinical investigations for drugs and medical devices.

For example, FDA created a uniform system of human subject protection when it initially amended its regulations governing human subject protection in 1981 (46 FR 8942). In revising part 50, FDA aimed to: (1) Address the informed consent provision included in the device amendments, (2) create a uniform set of Agency-wide informed consent standards for more effective administration of the Agency's bioresearch monitoring program, (3) implement recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and (4) harmonize FDA's rules with those of HHS (then the department of Health, Education, and Welfare). Indeed, the preamble expressed the Agency's intent to adopt a single standard that reflected the most current congressional thinking on informed consent and the important ethical principles and social policies underlying the doctrine of informed consent (46 FR 8942 at 8943).

Requiring a statement regarding the registry databank for informed consent documents and processes for only applicable clinical drug trials but not applicable clinical device trials would create a disparity in FDA's policy on human subject protection. This disparity could result in confusion among those who conduct such clinical trials over what is required in informed consent documents and processes, especially in the cases of applicable clinical trials involving both a drug and device or for investigators conducting applicable clinical trials of both types of regulated products.

Thus, although section 801(b)(3)(A) of FDAAA requires the statement regarding the clinical trial registry databank for informed consent documents and processes only for applicable drug clinical trials conducted under section 505(i) of the FD&C Act, under its general authority to issue regulations for the efficient enforcement of the FD&C Act (section 701(a) of the FD&C Act), FDA is requiring all applicable clinical trials, including applicable device clinical trials, to include this new statement in informed consent documents and processes. Requiring an additional statement regarding the inclusion of clinical trial information in the registry databank to be included in the informed consent documents and processes for all applicable clinical trials is the most efficient method of implementing the statutory mandate. To prevent confusion that might result from different requirements for informed consent for applicable clinical drug and device trials and implement the congressional purpose reflected in FDAAA, we will apply the same standards regarding elements of informed consent to applicable clinical drug and device trials by amending § 50.25 to include a new paragraph (c) which requires a statement about the registry databank in informed consent discussions and documents for all applicable clinical trials under section 801 of FDAAA.

The Agency has several options available for enforcing the new informed consent requirement. The authority to issue regulations for the protection of human subjects is accompanied by the authority to impose penalties for violations of such regulations. Specifically, section 301(e) of the FD&C Act (21 U.S.C. 331(e)) makes the "failure to establish or maintain any record, or make any report, required under section * * * 505(i) * * *" and the "failure or refusal to comply with any requirement prescribed under section * * * 520(g)" prohibited acts. The FD&C Act and implementing regulations allow FDA to seek administrative, civil, and criminal penalties for violations of section 301 of the FD&C Act. 21 U.S.C. § 303(a); §§ 312.44(b)(1)(ix), 312.70(a), 812.30(b)(4), 812.119(a), 56. 121(b).

VI. Environmental Analysis

The Agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this final rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule is expected to impose costs of about $3 per clinical trial participant or $611 to $1,061 per trial protocol, the Agency certifies that it will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $135 million, using the most current (2009) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

B. The Final Rule

On December 29, 2009, FDA published a proposed rule that would require that the informed consent documents for applicable drug and device clinical trials include a statement that applicable clinical trial information has been or will be submitted to the NIH/NLM for inclusion in the statutorily required clinical trial databank. As it pertains to applicable drug clinical trials, the final rule would implement a requirement of FDAAA. As discussed previously in this preamble, FDA also requires that the same statement be included in the informed consent documents for applicable device clinical trials.

The proposed rule included an analysis of impacts as required by Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). FDA received many public comments concerning its estimated costs and benefits for the proposed rule. As a result of the review and consideration of these and other comments to the proposed rule, FDA has made changes to both the codified final rule and its analysis of impacts section.

C. Need for the Final Rule

The need for this rule arises from section 801(b)(3)(A) of FDAAA. It requires that the current regulations for informed consent documents and process be amended to include a statement that clinical trial information from the clinical investigation has been or will be submitted to the NIH/NLM clinical trial registry databank. FDA has decided that revising the general informed consent section is the appropriate course by which to fulfill the requirements of the statute, and will provide the pertinent information and protection for clinical trial participants.

D. Public Comments Concerning Impacts Analysis

Several comments objected to the inclusion of the informed consent statement for various reasons. Some believed the statement would cause confusion or anxiety to the participants. Others believed it would distract the participants from focusing on the substantive issues concerning the study that would affect one's decision to participate in the study. Some comments stated that the overall effect would be a reduced participation rate for prospective participants. No estimates of the size of this reduced participation rate were submitted. Additional comments questioned whether any relevant or valuable information could be acquired from an informed consent statement that takes less than 1 minute to read and discuss, resulting in less benefit to the participant than the administrative costs to the investigator.

FDA acknowledges that additional time will be required to read and, if necessary, discuss the statement that FDAAA mandates be included in the informed consent documents and process. FDA does not agree, however, that the benefit of the statement to the participant is directly related to the time it takes to read and discuss the statement. Further, FDA maintains that the benefits of the informed consent statement would be difficult to estimate with any certainty, making a meaningful comparison of benefits to costs impractical. FDA also has revised the statement to make it shorter and easier to understand by deleting those terms that could be expected to cause anxiety and confusion. FDA believes that in doing so it has reduced the theoretical possibility that the statement would cause some participants to abandon the study as much as possible while still fulfilling the FDAAA mandate.

E. Benefits of the Final Rule

FDA published a qualitative explanation of the expected benefits to clinical trial participants in its 2009 proposed rule. FDA received some public comments that agreed with the expected benefits. Others disagreed, criticizing the proposed rule for not educating the public at large about the clinical trial registry databank. Some proposed that FDA undertake a public education campaign to broaden awareness of the clinical trial registry databank. That policy option, however laudable, was not included in the FDAAA mandate concerning updating FDA's regulations concerning informed consent documents and process. While an educational campaign is not the subject of this rulemaking, there will be other opportunities for improving awareness of the NIH clinical trials databank. The comments as a whole did not contain any arguments that convinced FDA that it should amend its initial explanation of benefits. As a result, FDA restates the expected benefits for this final rule.

The rule would increase the transparency of clinical trials by increasing participant and patient awareness of the existence of the clinical trials databank and those trials that are registered in the databank. By helping to create a system of checks and balances through which participants, patients, and health care providers are encouraged to check whether information about a trial of interest is registered in the databank, it also would provide greater accountability of clinical trial investigators for outcomes and adverse events, thereby raising confidence in the validity of the research process. Last of all, it would encourage physicians and patients to obtain more information in order to make more educated treatment decisions. FDA has not attempted to quantify these benefits, but believes that the overall effect of the rule on public health would be positive.

F. Costs of the Final Rule

FDA estimated the total costs of the proposed rule to both industry and the

clinical trial participant population to range from $688,000 to $2,398,000 annually. This equated to $98 to $342 per trial protocol, or about $0.48 to $0.96 per clinical trial participant. These costs included labor costs for both the investigator and the trial participant, as well as document preparation costs and paper materials costs. The cost of government oversight was not expected to be significant. For the most part, the public comments on the proposed rule did not address the structure of the cost analysis (except IRB review costs). FDA retains much of the cost analysis of the proposed rule for the final rule.

1. Labor Costs

The costs of the final rule derive from complying with the requirement to add another statement to the informed consent documents and the additional time that medical professionals and clinical trial participants spend reading and discussing this statement.

We have revised the final cost estimate to account for the administrative costs for companies involved in pharmaceutical, biologic, and medical device research and manufacturing, and administrative costs for IRB oversight. These additional labor costs are due to the administrative review of the rule and the determination of compliance responsibilities. All companies involved in this would incur some labor costs, regardless of the frequency with which they undertake clinical trials. Census data from 2002 list 5,666 companies in the seven North American Industrial Classification System (NAICS) categories that would be subject to this rule. FDA estimates that each could expend about 2 hours to review the final rule and determine any changes it needs to make to its internal administrative policies due to this rule. The pharmaceutical and medicine manufacturing category of the NAICS lists the hourly wage for a manager in this category at about $54. A 35 percent adjustment to this figure for employee benefits results in total hourly compensation costs of about $73. A one-time 2 hour review for each company would result in compliance costs of almost $147 per company, and a total of about $830,000 for the industry. This equates to an annualized cost (over 5 years at a 7 percent discount rate) of about $202,000 for the entire industry. These estimates may overstate true compliance costs for review of the rule since those companies that rarely sponsor clinical trials on even an occasional basis may not expend as much labor as those who do so more frequently.

For the proposed rule, FDA estimated that it receives about 7,000 clinical trial protocol submissions annually for applicable clinical trials that would be subject to this final rule, with the vast majority of the submissions to the FDA's Center for Drug Evaluation and Research (CDER). The public comments did not address the size of this estimate. However, further analysis of the data upon which the estimates were made shows that up to 30 percent of the CDER protocols may be for phase 1 clinical trials which would not be subject to the final rule. FDA has adjusted the estimated number of CDER trial protocols accordingly, which results in a reduction of the total trial protocols estimate to 5,146. FDA estimates of average numbers of participants per clinical trial vary greatly across FDA Centers, from single-patient INDs to vaccine trials with over 25,000 participants. Published data on average number of participants per trial, therapeutic area, suggests that the average number of participants in phase 1, 2, and 3 clinical trials of pharmaceuticals, biotech, and medical device products may range from about 200 to 360.[1] FDA did not receive any comments on this estimate of the average number of participants per clinical trial, and retains it for the analysis of the final rule.

Compliance with the rule would require that the informed consent documents contain the required statement concerning the clinical trial's inclusion in the clinical trial registry databank and provide for any additional discussion concerning this statement between participants and the medical gsgt6egiicalormedng trureny additional

[1] *Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2008/2009,* Parexel International Corp., copyright 2008, p. 160. The average number of participants (not weighted by therapeutic area) in phase 1, 2, and 3 clinical trials in 2006 was 27, 141, and 444, respectively. The unweighted average of these numbers is 204. As an upper bound, FDA uses the average of the numbers representing the therapeutic area with the largest average number of participants in each of the three clinical phases, which would tend to overstate the average size of participants. This upper bound is calculated at 360 participants per trial protocol.

TABLE 1—COSTS OF INFORMED CONSENT PROPOSED RULE—Continued

Cost factor	Annual cost
Total Costs	3,143,000–5,458,000

[1] This is a one-time cost of $830,000 annualized over 5 years at 7 percent.

Some clinical trial participants are compensated for their participation in trials. Whether an individual participant receives compensation or not, the additional time spent by all participants to read and discuss the new informed consent statement represents a social cost of the rule. Using the median U.S. wage rate of $15.57 per hour, a clinical trial participant would be expected to incur a cost of $0.78 for the 3 minutes to read and, if necessary, discuss the proposed informed consent statement. On an annual basis over the 5,146 clinical trials, this would amount to about $0.80 million to $1.44 million.

Comments to the proposed rule included a criticism that FDA had failed to account for the costs to IRB for its oversight role of the new statement. FDA agrees that the new informed consent statement will require an additional amount of oversight from IRBs. FDA has added to its cost elements a labor cost for the effort of the IRBs to determine that the statement has been added to the model templates for informed consent documents. Although IRBs can have many members, in wT*(to re7houg4ropos.n3esm(C)Tj8 0h)TjT*(IT*(Ih re74l/TT8)Tj0.2265jT*(addA has added 414os.iatesT 5requirnseycost)TjT*wag[(...4, IRBs. sary, discnfisdry, SBA) sizi tt.80ardagew sscu T snehe co latsmscu eorItie.. Ev notakdate for itsinincaccoumoueTtemmug4rhe staririan U.S.ett.blishT*wr h

[2] U.S. Department of Labor, Bureau of Labor Statistics, May 2009 National Occupational Employment and Wage Estimates United States, p. 8.

multiple applicable clinical trials in the same year. For large firms that would administer the informed consent documents for 10 separate trials, the cost would range from $6,110 to $10,610 per year. Using 2002 Census data, the average value of shipments for establishments in these industries with one to four employees ranged from $244,000 to $824,000 according to the Census of Manufacturers. Assuming that such small operations had one applicable clinical trial administered each year, the costs of the proposed rule would represent, at most, 0.43 percent of the annual value of shipments. For establishments with 50 or more employees, the compliance costs would represent 0.11 percent or less of the value of shipments even with 10 applicable clinical trials administered annually. For establishments with 100

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10. Institutional Review Board: Management and Function (edited by Bankert, E. A. and R. J. Amdur), 2d Ed., 2006 (Chapter 6–1, *The Institutional Review Board's Role in Editing Consent Documents,* Pensha, R. L., pp. 199–201 and Chapter 6–2, *The Consent Documents,* Brown, A., pp 202–204).

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