Guidance for Industry

Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

DRAFT GUIDANCE

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For questions regarding this draft document, contact Terry Toigo, 301-827-4460.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Procedural

Revision 1

Guidance for Industry

Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

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Guidance for Industry[1] Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors who will be submitting information to the Clinical Trials Data Bank. The data bank was established as required under section 113 of the Food and Drug Administration Modernization Act of 1997 (Modernization Act). This guidance updates and replaces the March 2002 guidance for industry of the same title to include assistance for sponsors who will be submitting information required by the Best Pharmaceuticals for Children Act (Public Law 107-109) (BPCA). Additional updates on procedural issues not related to the BPCA will be discussed in future revisions to this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Section 113 of the Modernization Act creates a public resource for information on studies of drugs, including biological drug products, to treat serious or life-threatening diseases and

[1] This guidance has been prepared by the Implementation Team for section 113 of the Food and Drug Administration Modernization Act of 1997, including individuals from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), at the Food and Drug Administration.

Paperwork Reduction Act Public Burden Statement: According to the Paperwork Reduction Act of 1995, a collection of information should display a valid OMB control number. The valid OMB control number for this information collection is 0910-0459 (expires 03/31/2004). The time to complete this information collection is estimated to average 284 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection.

conditions conducted under FDA's investigational new drug (IND) regulations (21 CFR part 312). Section 113 of the Modernization Act, enacted November 21, 1997, amends section 402 of the Public Health Service Act (42 U.S.C. 282). It directs the Secretary of Health and Human Services, acting through the Director of the National Institutes of Health (NIH), to establish, maintain, and operate a data bank of information on clinical trials for drugs to treat serious or life-threatening diseases and conditions. The Clinical Trials Data Bank is intended to be a central resource, providing current information on clinical trials to individuals with serious or life-threatening diseases or conditions, to other members of the public, and to health care providers and researchers. Specifically, section 113 of the Modernization Act requires that the Clinical Trials Data Bank contain (1) information about Federally and privately funded clinical trials for experimental treatments (drug and biological products) for patients with serious or life-threatening diseases or conditions, (2) a description of the purpose of each experimental drug, (3) patient eligibility criteria, (4) a description of the location of clinical trial sites, and (5) a point of contact for patients wanting to enroll in the trial. Section 113 of the Modernization Act requires that information provided through the Clinical Trials Data Bank be in a form that can be readily understood by the public. 42 U.S.C. 282(j)(3)(A).

The BPCA, signed by the President on January 4, 2002, requires a description of whether, and through what procedure, the manufacturer or sponsor of an IND will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children.

The NIH, through its National Library of Medicine (NLM) and with input from the FDA and others, developed the Clinical Trials Data Bank. The first version of the Clinical Trials Data Bank was made available to the public on February 29, 2000, on the Internet.[2] At that time, the data bank included primarily NIH-sponsored trials.

In response to the Modernization Act's requirements for a data bank, FDA made available two draft guidances and a final guidance. The first draft guidance provided recommendations for industry on the submission of protocol information to the Clinical Trials Data Bank.[3] It included information about the types of clinical trials for which submissions are required under section 113 of the Modernization Act, as well as the content of those submissions.

The second draft guidance addressed procedural issues, including how to submit required and voluntary protocol information to the Clinical Trials Data Bank, as well as issues related to submitting certification to the Secretary that disclosure of information for a particular protocol would substantially interfere with the timely enrollment of subjects in the clinical investigation[4] The second draft guidance also proposed a time frame for submitting the information. A final

[2] See http://clinicaltrials.gov

[3] See http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gl.pdf

[4] See 66 FR 35798 and http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gd.pdf

guidance, made available on March 18, 2002,[5] combined the two draft guidances into a single guidance.

This updated guidance includes new recommended procedures for submitting details, as required by the BPCA, about single-patient use and expanded access use.

III. REQUIREMENTS UNDER SECTION 113 OF THE MODERNIZATION ACT FOR IND SPONSORS

A. What information must I submit to the Clinical Trials Data Bank?

Section 113 of the Modernization Act requires you to submit information to the data bank about a clinical trial conducted under an investigational new drug (IND) application if it is for a drug to treat a serious or life-threatening disease or condition and it is a trial to test effectiveness (42 U.S.C. 282(j)(3)(A)). If you wish, you can also provide information on trials not designed to assess effectiveness or for drugs to treat conditions not considered serious or life-threatening.

Section 113 of the Modernization Act requires that you submit a description of the purpose of each experimental drug, patient eligibility criteria for participation in the trial, a description of the location of clinical trial sites, and a point of contact for those wanting to enroll in the trial. Section 113 requires that the data bank provide this information in a form that can be readily understood by members of the public (42 U.S.C. 282(j)(3)(A)).

The BPCA amended 42 U.S.C. 282 (j)(3)(A) to require that you submit a description of whether, and through what procedure, you (the manufacturer or sponsor of a clinical investigation of a new drug) will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children.[6]

To ensure that information available through the Clinical Trial Data Bank is in a form that is readily understood, we have established four data elements, which are listed below. The data elements are made up of the following data fields: (1) descriptive information, (2) recruitment information, (3) location and contact information, and (4) administrative data. We have established the Protocol Registration System (PRS), a Web-based data processing program, to facilitate collection of this information for the data bank. The four data elements, which are listed below, as well as definitions applicable to the PRS, can be viewed at *http://prsinfo.clinicaltrials.gov/*.

1. Descriptive Information

Brief Title (in lay language)
Brief Summary (in lay language)
Study Design/Study Phase/Study Type
Condition or Disease

[5] See 67 FR 12022 and http://www.fda.gov/OHRMS/DOCKETS/98fr/00d-1033_gdl0003.pdf
[6] See 42 U.S.C. 282(j)(3)(A) at http://www.fda.gov/opacom/laws/pharmkids/contents.html.

Intervention
Single-patient/expanded access use

2. Recruitment Information

Study Status Information including

- Overall Study Status (e.g., recruiting, no longer recruiting)
- Individual Site Status

Eligibility Criteria/Gender/Age

3. Location and Contact Information

Location of Trial
Contact information (includes an option to list a central contact person for all trial sites)

4. Administrative Data

Unique Protocol ID Number
Study Sponsor
Verification date

To verify the existence of an IND and to assist in administrative tracking, we ask that you also include in your submission the IND number and serial number and designate whether the IND is located in the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). This administrative information is in a separate data field and will not be made public.

B. When should I begin submitting clinical trial information?

Section 113 of the Modernization Act requires that sponsors submit information no later than 21 days after the trial is opened for enrollment[7] (42 U.S.C. 282(j)(3)). Section 113 does not specify when sponsors must submit information about clinical trials that are existing and ongoing. To provide a transitional period for sponsors of clinical trials that are currently ongoing and expected to continue enrolling patients for more than 45 days, we ask that you submit information within 45 days after this guidance is made available through the *Federal Register*. We encourage you to submit information through the PRS for inclusion in the data bank as soon as possible.[8]

[7] Section 113 says "not later than 21 days after the approval of the protocol." Because the Agency does not approve protocols, we have interpreted this to mean within 21 days after the trial is open for enrollment.

[8] See *http://prsinfo.clinicaltrials.gov*.

C. Can I submit my information at specified intervals rather than on a rolling basis?

As discussed above, you must submit information about new protocols open for enrollment within 21 days after the trial is open for enrollment (42 U.S.C. 282(j)(3)), and we request that you submit information about existing ongoing trials within 45 days after this guidance is published. Supplemental information can be submitted at 30-day intervals. Such information includes amendments to the protocol with respect to one of the data elements, or interruptions, continuations, or completion of enrollment for a study. Protocol changes related to eligibility or status information, such as routine opening and closing of trial sites, can be made at 30-day intervals. FDA strongly encourages you to update information about trials that are unexpectedly closed (e.g., clinical hold) within 10 days after the closing or sooner if possible.

To ensure that the information available through the data bank is timely and accurate, FDA also encourages you to review, verify, and update all active protocol records on a semi-annual basis, at a minimum.

D. What is a trial for a serious or life-threatening disease or condition?

FDA has defined serious and life-threatening diseases and conditions in previous documents. Most recently, FDA discussed issues related to products intended to treat serious or life-threatening diseases and conditions in the guidance for industry on *Fast Track Drug Development Programs - Designation, Development, and Application Review* (November 1998).[9] In that guidance, we stated that all conditions meeting the definition of life-threatening, as set forth at 21 CFR 312.81(a), would also be serious conditions. The term *life-threatening* is defined as (1) diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and (2) diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival (21 CFR 312.81(a)). All references in this document to serious diseases or conditions include life-threatening diseases and conditions.

As FDA reiterated in the *Fast Track Guidance*, the seriousness of a disease is a matter of judgment, but generally is based on such factors as survival, day-to-day functioning, and the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. For example, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's disease, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Furthermore, many chronic illnesses that are generally well managed by available therapy can have serious outcomes. For example, inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses, and many other diseases can be serious in some or all of their phases or for certain populations.

[9] CDER guidances are available at http://www.fda.gov/cder/guidance/index.htm.

Any investigational drug that has received fast track designation would be considered a drug to treat a serious disease or condition.[10] Information on effectiveness trials for drugs that have received fast track designation would qualify for submission to the Clinical Trials Data Bank.

E. What is a trial to test effectiveness?

Not all trials carried out under 21 CFR part 312 are trials to test effectiveness. FDA considers all phase 2, phase 3, and phase 4 trials with efficacy endpoints as trials to test effectiveness.[11]

F. Which trials are provided to the public through the Clinical Trials Data Bank?

Section 113 of the Modernization Act requires sponsors to submit information about clinical trials of experimental treatments for serious or life-threatening diseases and conditions when conducted under the IND regulations (42 U.S.C. 282(j)(3)(A)). Such information can be submitted at any time with the consent of the protocol sponsor, and must be submitted within 21 days after a trial to test effectiveness begins. In addition, section 113 of the Modernization Act states that information on all treatment IND protocols and all Group C protocols[12] must be included in the Clinical Trials Data Bank.

There are situations in which there may be patients with the disease or condition for which the drug is being developed who are not adequately treated by existing therapy, who do not meet the eligibility criteria for enrollment, or who are otherwise unable to participate in a controlled clinical study. In these situations, you may have initiated an expanded access protocol or be willing to provide the drug to an individual patient through a single-patient IND or protocol exception.[13] The BPCA requires that you submit a description of whether, and through what procedure, you will respond to requests for protocol exception for single-patient and expanded access use of the investigational drug, particularly in children.

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[10] That a drug is intended to treat a serious or life-threatening disease or condition, however, does not mean that it fills an unmet medical need and qualifies for fast track designation under section 506 of the Food Drug and CosmeticAct (21 U.S.C. 356).

[11] Listing a trial in the Clinical Trials Data Bank is not a guarantee that the trial design is considered adequate to support approval of a drug, nor does it reflect any judgment on the conduct, analysis, or outcome of the study.

[12] "Group C protocols" refers to investigational drugs designated by FDA for the treatment of specific cancers. These drugs have reproducible efficacy in one or more specific tumor types. Such a drug has altered or is likely to alter the pattern of treatment of disease and can be safely administered by properly trained physicians without specialized supportive care facilities. *See* National Cancer Institute Handbook for Investigators, Appendix XV, "Policy for Group C Drug Distribution," http://ctep.info.nih.gov/HandbookText/Appendix_XV.htm#Proc_Mgmt_GrpC_Prot.

[13] There are a number of mechanisms FDA has used to provide access to promising investigational therapies. In addition to treatment INDs and treatment protocols, which are described in FDA regulations, expanded access mechanisms fall under a variety of terms, such as single patient INDs, emergency INDs, protocol exemptions, special exceptions, open label extensions, and parallel track. FDAMA has codified certain FDA regulations and practices regarding expanded patient access to experimental drugs. FDA is reviewing current regulations and practices to assure coordination with FDAMA.

For protocols not specifically mentioned above, sponsors should review each protocol submitted to an IND to determine if the protocol is for a serious disease or condition and if it is a trial to test effectiveness. If the protocol meets these criteria, the sponsor must submit information about the trial to the Clinical Trials Data Bank, ***unless*** the sponsor provides detailed certification to FDA that such a disclosure would substantially interfere with the timely enrollment of subjects in the investigation (42 U.S.C. 282(j)(3) and (j)(4)). Sponsors with questions on whether protocols meet the criteria for submission to the Clinical Trials Data Bank are encouraged to contact the appropriate review division for additional guidance.

G. Must I include information about foreign trial sites?

Yes, you must include information about foreign trials when those trials are conducted under an IND submitted to FDA and the trial meets the criteria for submission to the Clinical Trials Data Bank. Section 113 of the Modernization Act requires sponsors to submit information about specified clinical trials that are "under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act," which are FDA's IND regulations (42 U.S.C. 282(j)(3)). Sponsors may voluntarily conduct a foreign trial under the IND regulations. Sponsors are not required to submit information to the Clinical Trials Data Bank when a foreign trial is not conducted under an IND.

IV. IMPLEMENTATION ISSUES

A. How do I submit information to the Clinical Trials Data Bank?

To facilitate the submission process, we have established the Web-based PRS at *ClinicalTrials.gov*. The system allows for entry of required and voluntary information about clinical trials. You or your designee can initiate submission of clinical trial information to *ClinicalTrials.gov* by completing a registration form at *http://prsinfo.clinicaltrials.gov/*. After you have entered the data, the PRS generates a receipt for use by sponsors. An electronic copy of the receipt will be sent to the FDA.

B. What information about trial sites must be included?

Section 113 of the Modernization Act requires sponsors to submit a description of the location of trial sites and a point of contact. To ensure an adequate description, we recommend that you provide for each individual trial site the full name of the organization, city, state, postal code, and country where the protocol is being conducted; and a central contact name and phone number. You can also provide the names and phone numbers of individual site contacts.

C. How long does it take for information to be made available on ClinicalTrials.gov?

Studies will be made available to the public through *ClinicalTrials.gov* within 2 to 5 days after submission by the sponsor.

D. How long will information about studies remain available through ClinicalTrials.gov?

NLM intends to maintain the Data Bank as a long-term registry of clinical trials. Therefore, in addition to information about open trials, information about closed trials will also be available through *ClinicalTrials.gov,* even after accrual and analysis are completed and the product is approved.

E. Can information be transferred from a sponsor computer to the PRS?

Yes. Information can be transferred according to the format specified by the PRS. The PRS has a mechanism for uploading and downloading XML-formatted protocol records. Instructions for transferring information are provided at *http://prsinfo.clinicaltrials.gov/*

F. Can intermediaries acting on behalf of a sponsor submit data?

Yes. For example, in some cases a sponsor might want to contract with an information management company to serve as an intermediary in preparing data for inclusion in *ClinicalTrials.gov*. The information management company, when authorized by the sponsor, could act on behalf of the sponsor for this purpose.

G. Can sponsors designate multiple individuals to be data providers?

Yes. When sponsors register to become a PRS data provider, they will be given information, including instructions, for creating additional users for their accounts. A sponsor can control access to the account by designating users and administrators for the account.

H. What happens to the information submitted to the Clinical Trials Data Bank?

Except for the IND number, serial number, and FDA center designation, all information submitted through the PRS is made available to the public at *http://clinicaltrials.gov*.

I. Can I submit other information to the Clinical Trials Data Bank?

Yes. PRS is designed to permit you to submit more detailed information about a protocol. Additional data fields (e.g., projected enrollment) and their definitions are included in the PRS. You also can submit protocol information about other clinical trials under IND, including trials for a disease or condition that is not serious or any trial that is not designed to test effectiveness. Finally, you can submit information about results of a trial. This information, which, according to the structure of the Clinical Trials Data Bank, is to come from the published literature, should be linked by including the unique MEDLINE identifier for citations of publications. You can use the *link* section provided to allow pointers to Web pages directly relevant to the protocol. If you link to other Web pages from your entries, you should ensure that the links do not misbrand your products, for example, by promoting the products before the product or an

indication is approved. (See 21 U.S.C. 321(n), 331(a)(b)(c)(d), 352(a)(n) *http://www.fda.gov/opacom/laws/fdcact/fdcact1.htm*.) When inputting links to other web pages, the database will instruct you that the links should be directly relevant to the protocol, and that you should not link to sites whose primary goal is to advertise or sell commercial products or services.

J. Should I continue submitting information to the ACTIS and PDQ databases?

No. All information for AIDS and cancer protocols that meet the requirements of section 113 of the Modernization Act must now be submitted to *ClinicalTrials.gov* through the PRS. Data from the current AIDS Clinical Trials Information System (ACTIS) and Physician's Data Query (PDQ) databases are included in *ClinicalTrials.gov*. Information from the Rare Diseases and National Institute of Aging Databases is also included in *ClinicalTrials.gov*.

K. Are there exemptions for submitting clinical trials information?

Information about an investigation will not be included in the data bank if you provide a detailed certification to the Secretary of Health and Human Services that disclosure of such information would substantially interfere with timely enrollment of subjects in the clinical trial and the Secretary does not disagree. If there is disagreement, the Secretary will provide a detailed written determination that such disclosure would not substantially interfere with such enrollment (42 U.S.C. 282(j)(4)).

FDA has not identified specific instances when disclosure of information would substantially interfere with enrollment of subjects in a clinical investigation. We solicited comments on this topic for the purpose of including a listing of acceptable reasons for certification in the final guidance. We received no comments. Therefore, if you identify a specific instance when disclosure of information would interfere with enrollment of subjects in a clinical investigation, FDA will consider your request on a case-by-case-basis.

All requests for exemption should be forwarded to Director, Office of Special Health Issues, Office of Communications and Constituent Relations, Office of the Commissioner, HF-12, 5600 Fishers Lane Rockville, MD 20857, or by email at *113trials@oc.fda.gov*, or by fax at 301-443-4555.

L. Is Institutional Review Board preapproval of the protocol listing required?

No. Section 113 of the Modernization Act does not require prior IRB approval when submitting this information to the Clinical Trials Data Bank. Current FDA guidance recommends that IRB review of listings need not occur when, as here, the system format limits the information provided to basic information, such as title, purpose of the study, protocol summary, basic eligibility criteria, study site locations, and how to contact the site for further information. [14]

[14] The 1998 update of *Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators* provides guidance on IRB review and approval of listings of clinical trials on the Internet. See http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting.

M. Will FDA monitor compliance?

A copy of the protocol listing in *ClinicalTrials.gov* will be sent to the FDA. FDA's Office of Special Health Issues initiated a pilot educational program in 2002 that included a component to evaluate compliance. The primary objective of the pilot program is to educate sponsors about the existence of the guidance document and the availability of the online PRS data entry tool. The secondary objective of the pilot program is to evaluate the success of the educational initiative. The pilot program will measure the number of protocols (voluntary and required) made available through the *ClinicalTrials.gov* database. Data from the completed project will help senior FDA officials assess the need for further efforts to facilitate or perhaps compel participation in *ClinicalTrials.gov.*

N. What information about protocol exceptions, single-patient use, and expanded access protocols must I include?

There are situations in which there may be patients with the disease or condition for which the drug is being developed who are not adequately treated by existing therapy, who do not meet the eligibility criteria for enrollment, or who are otherwise unable to participate in a controlled clinical study. In such a situation, you may wish to provide the drug to a patient through a protocol exception/exemption, single patient IND, or expanded access protocol.

The BPCA amended Section 113 of the Modernization Act to require that you submit, in addition to the information already included in the Clinical Trials Data Bank, a description of whether and through what procedure you will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded access use of the investigational drug, particularly in children.

The PRS includes a mechanism for providing information about protocol exceptions, single-patient INDs, and expanded access protocols. In order to comply with the BPCA amendment to section 113 of the Modernization Act, we suggest that you address the following two questions and provide a brief description as described below. This information is required for each new protocol that is listed in the data bank; we encourage you also to provide this information for protocols currently open to enrollment.

- Is this investigational drug available for use in adults through a protocol exception, single-patient IND, or expanded access protocol?
  Yes No

- Is this investigational drug available for use in children through a protocol exception, single-patient IND, or expanded access protocol?
  Yes No

- Brief description of the procedure for responding to requests for expanded access, including contact number and/or email address.