KING & SPALDING

Client Alert

FDA & Life Sciences Practice Group

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HHS Issues Notice of Proposed Rulemaking for Clinical Trials Registration and Results Submission to ClinicalTrials.gov

On November 19, 2014, the Department of Health and Human Services (HHS) published, for a 90-day public comment period, a Notice of Proposed Rulemaking (NPRM) for Clinical Trials Registration and Results Submission.[1] The proposed rule clarifies requirements for registering and submitting results information for clinical trials that study FDA-regulated drugs (including biological products) and devices and are subject to section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which amended section 402(j) of the Public Health Service Act (the Act).[2] It also addresses expansion of the registry and results data bank by rulemaking, as required by section 402(j) of the Act.[3] **Comments on the HHS proposed rule are due by *February 19, 2015*.**

- Section 402(j) of the Act provides HHS with the authority to expand the requirements for information that must be submitted to the registry data bank to "to enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials" if the modifications meet the criteria of improving and not reducing the statutorily specified registration information.

- It separately provides HHS with the authority for—and explicitly mandates—the expansion of both the registry and results data bank "to provide more complete results information and to enhance patient access to and understanding of the results of clinical trials." Among the proposed new requirements is the submission of results information, including adverse events, for applicable trials of drugs and devices that previously have not been approved, licensed, or cleared by FDA for any use.

In a separate Guide Notice published on November 19th, the NIH proposed a complementary draft policy pertinent to all NIH-funded clinical trials, regardless of whether or not they are subject to FDAAA. The Guide Notice will not be addressed in this Client Alert.

Background

Section 801 of FDAAA, which was enacted on September 27, 2010, expanded the requirements for submission of clinical trial information to the publicly accessible database ClinicalTrials.gov, which is overseen by the

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National Library of Medicine under the National Institutes of Health (NIH). The legal requirements for submitting registration and results data are applicable to a "*Responsible Party*," who is defined as the sponsor of an Applicable Clinical Trial or the principal investigator, if designated by sponsor for this obligation. In addition, the statute identifies "*Applicable Clinical Trials*" as clinical studies that, in general, are prospective controlled clinical trials that study drugs and medical devices subject to FDA regulation where the patient is assigned to an intervention, but excluding Phase 1 studies of drugs and feasibility studies of devices. (In addition, the statutory definition of Applicable Device Clinical Trial includes pediatric postmarket surveillances of devices required by FDA, regardless of whether the surveillance is a clinical trial.)

Stages of implementation. Section 402(j) of the Act implemented the new requirements in stages, beginning with the requirement for registration on December 26, 2010 for Applicable Clinical Trials that were ongoing as of that date and no later than 25 days after enrollment of the 1st subject for trials initiated thereafter. Since September 27, 2008, the submission of "*Basic Results*" information has been required, followed by "*Adverse Event*" data submission requirements since September 27, 2009. Unlike the registration requirements, which apply to all Applicable Clinical Trials, the submission of basic results, including adverse events, is currently mandatory only for Applicable Clinical Trials of drugs and devices that are already approved, licensed, or cleared by FDA for any use. The elements of information that are currently required for the submission of registration and basic results, including adverse events, are specified in detail in the statute.

The final stage required by the Act is rulemaking to address the "*Expanded Registry and Results Data Bank.*"[4] When expanding requirements for the information that summarizes clinical trial results, the Act requires consideration whether results and adverse event information must be also be submitted for Applicable Clinical Trials of ***unapproved, unlicensed, or uncleared drugs and medical devices***. The Act also requires consideration whether the specified time periods for submission of certain information should be modified, and whether the expanded requirements are to include (1) a non-technical summary intended for patients and/or a technical summary of the trial and its results "if such types of summary can be included without being misleading or promotional" and (2) the full clinical protocol for the trial "as may be necessary to help evaluate the results of the trial."

Overview of the Proposed Rule

HHS emphasizes that the NPRM does not change ***current*** requirements for registration and submission of basic results, including adverse events, for Applicable Clinical Trials. However, the proposed rule, if finalized, would make major changes to the current requirements; among these, the following six proposed modifications and additions are discussed in more detail in this Client Alert:

- Clarification of key terms and processes in the statute, including which trials are subject to the proposed regulations and who must submit information;
- Expansion of the data elements that must be provided at the time of registration;
- Creation of Expanded Access Records;
- Expansion of the requirement for reporting results to include Applicable Clinical Trials of unapproved, unlicensed, and uncleared products;
- Procedures for delaying the submission of results or requesting a "good cause" extension to the results submission deadline for good cause;
- Timely updating of information and corrections of errors (including falsified information).

Clarification of key terms and processes, including which trials must be registered and who must submit information.

- **Streamlined checklists to identify Applicable Clinical Trials that must be registered.** Subpart A of the proposed rule addresses General Provisions, including clarification of multiple, key terms in the statute. Subpart B addresses the requirements for Registration. Subpart B provides checklists, which amplify the definitions in Subpart A, to identify those Applicable Clinical Trials of drugs and devices that must be registered.

    - The definitions together with the checklists help to clarify that Applicable Clinical Trials are those that study a drug or a medical device that is subject to FDA regulation under the Federal Food, Drug, and Cosmetic Act if the product were to be marketed in the United States and where (1) at least one clinical trial facility location is within the U.S. or one of its territories, (2) the trial studies a drug or device manufactured in the U.S. or one of its territories and exported for study in another country, ***or*** (3) the clinical trial has an FDA IDE or IND number. Thus, the proposed rule helps to clarify that Applicable Clinical Trials of FDA-regulated drugs and medical devices may include, but are not limited to, trials that are conducted under an FDA-approved Investigational New Drug (IND) or Investigational Device Exemption (IDE) application.

    - In addition, the clinical trials that must be registered must meet each of these additional criteria: (1) the study type is interventional (*i.e.*, the subject is prospectively assigned to the intervention), (2) the primary purpose is other than a feasibility study (for a medical device) or a phase 1 study (for a drug), and (3) the study is controlled (*i.e.*, the number of arms is two or more ***or*** it is a single-arm controlled study, such as a single-arm study that is to be compared against an historical control or a performance standard). The proposed rule also clarifies the requirements for registration of a pediatric postmarket surveillance of a device, even if it is not a clinical trial.

- **Who must submit information.** The proposed rule provides detailed clarification of the requirement that the "Responsible Party" who must submit both registration and results information is the sponsor or sponsor-investigator of the trial, as defined in 21 C.F.R. 50.3, unless this responsibility is delegated by the sponsor to a principal investigator. The proposed rule and its preamble clarify that, if a principal investigator is to be designated by the sponsor as the Responsible Party, that investigator must be responsible for conducting the trial at all sites if it is a multi-site trial, have full access to and control over the data, have the right to publish the results, and the ability to meet all of the requirements for submission of information (including access to accurate information held by the sponsor, such as the intent to pursue FDA approval or clearance of a product or a new use of the product and the date of such approval or clearance). If the sponsor does designate a principal investigator as the Responsible Party, the proposed rule would require formal notification of this designation, as well as acknowledgement by the investigator of acceptance of this obligation in the ClinicalTrials.gov record. In aggregate, the detailed descriptions of the conditions that must be met for an investigator to be designated by the sponsor as the Responsible Party appear to be intended to avoid duplicative registration submissions and ensure that there is a single organization or individual identified as the Responsible Party for a clinical trial, who then complies with all of the legal obligations.

Expansion of the data elements that must be provided at the time of registration.

Section 402(j) of the Act identifies 25 specific data elements that must submitted in the registration of an Applicable Clinical Trial, which are related to the categories of descriptive information, recruitment information, site location and

contact information, and administrative information. Exercising the authority provided in the Act to modify registration requirements by rulemaking if "a modification improves and does not reduce" such information, HHS proposes substantial modifications and additions to the required registration information and provides rationales for these modifications in the preamble. Among these proposed modifications, which HHS has determined would "improve clinical trial information available to the public and implement the requirements of the statute," the following are major proposed changes:

- **Increased structuring of data elements that must be entered for registration "to help the public use the data bank and compare entries."** In general, such structuring of data entries would require the Responsible Party to select and enter an option from a defined set of descriptive options for multiple elements, such as those related to study design and primary outcome measures. Among the new requirements would be the obligation, if applicable, to enter the IND or IDE number, any serial number assigned by the sponsor to that filing, and the name of the FDA center that issued the IND or IDE.

- **Entry of data to allow effective implementation, or compliance with, provisions of section 402(j).** As example, the proposed rule would require information about whether the product under study in a clinical trial is manufactured in the U.S. or one of its territories because the information is necessary in some circumstances for both the Responsible Party and HHS to determine if the study meets the definition of an Applicable Clinical Trial or would be considered a study for which data entry is a voluntary submission.

- **Additions to improve the quality and consistency of data and enable users to better search for, retrieve, and understand it.** As example, the proposed rule would require the Responsible Party to submit current and former names used to identify the drug or device, if such other names exist (*e.g.*, the name of the chemical compound, the brand name of an approved product, or an alias used during pre-market development).

- **Indication of the "ethical and scientific review status" of the clinical trial.** Under the proposed rule, the Responsible Party would be required to provide information as to whether the clinical trial is undergoing or has undergone review and approval by an institutional review board (IRB) or comparable human subjects protection review board, and if not, to specify whether such review and approval is not required by applicable law, regulation, or institutional policy.

- **Posting of registration information for applicable medical device trials—the conundrum.** Section 402(j) requires that registration information for applicable ***drug*** clinical trials be posted (*i.e.*, be made publicly available on the ClinicalTrials.gov website) no later than 30 days after it has been submitted. In contrast, the Act specifies that registration data for applicable ***device*** clinical trials of devices that previously have been approved or cleared by FDA be posted not later than 30 days after results information is required to be submitted. The preamble clarifies that HHS currently interprets this to mean "as soon as practicable."

  However, the Act specifies that for trials studying devices that previously have ***not*** yet been approved or cleared for any use, the registration information shall be posted not earlier than the date on which FDA approves or clears the device and not later than 30 calendar days after that date. The preamble of the NPRM notes that, whereas postponing the public disclosure of registration information for such devices may protect commercial interests of manufacturers, there are a number of situations in which manufacturers may wish to voluntarily make such information publicly available prior to these timelines, such as enhancing patient recruitment. HHS invites comments from the public on how, given the statutory language, registration information for applicable trials of devices that previously have not been approved or cleared may be made publicly accessible in ClinicalTrials.gov when the Responsible Party so chooses.

Creation of Expanded Access Records.

Section 402(j) of the Act requires submission of information on how to obtain expanded access to investigational drugs that are studied in Applicable Clinical Trials. (However, the Act does not require submission of information on how to obtain similar access to investigational devices.) If expanded access is available under Section 561 of the FDCA for a drug studied in an Applicable Clinical Trial, the proposed rule would require that the Responsible Party submit specific information via the creation of an "*Expanded Access Record*" in the registration data bank, which would be assigned a unique ClinicalTrials.gov identifier (*i.e.*, an NCT number). The creation of an Expanded Access Record would be applicable for programs for expanded access to investigational drugs for treatment use for "intermediate-size patient populations" and "widespread treatment use" but not for "individual patients," as described in 21 C.F.R. 312 Subpart I. The Responsible Party would be required to submit all elements specified in the regulation for Expanded Access Records, including descriptive information, eligibility criteria, status of drug availability via the expanded access program, contact information, and the IND number assigned by FDA to the expanded access program. In addition, the Responsible Party would be obligated to update certain information within time lines and correct erroneous or falsified information, similar to requirements pertinent to the registration of Applicable Clinical Trials. If an Expanded Access Record containing this information has already been submitted in conjunction with a different clinical trial, the Responsible Party entering registration information for the new clinical trial(s) of the same drug could link to the existing Expanded Access Record.

Submission of results: A new requirement to include Applicable Clinical Trials of unapproved, unlicensed, and uncleared drugs and devices.

Subpart C of the proposed rule addresses the submission of results. The most important change is that the proposed rule would extend the requirement for results submission to Applicable Clinical Trials of drugs and devices that are ***not*** approved, licensed, or cleared by FDA for any use. In the preamble, HHS "finds compelling the arguments in support of a requirement to submit results of Applicable Clinical Trials of unapproved, unlicensed, or uncleared products." Among the arguments presented by HHS are the opinions that systematic disclosure of results of all Applicable Clinical Trials mitigates bias in information made available to the public that "stems from selective disclosure of clinical trial results" and protects the safety of participants who volunteer to be in clinical trials by reducing the likelihood that others will unknowingly design trials that are unnecessary or unsafe (because similar trials have already been conducted and the data made public). Thus, for all Applicable Clinical Trials, the proposed rule would require the submission of tables of information summarizing demographics and baseline characteristics of the enrolled participants, the primary and secondary outcomes, and the results of scientifically appropriate statistical tests. Adverse event information would also be required to be submitted for all Applicable Clinical Trials. Similar to the default provisions in the statute, the proposed rule would require submission of information in table format summarizing, for each arm of the trial, all serious adverse events, as well as other adverse events with a frequency of five percent or more in any arm of the clinical trial, regardless of whether such events were anticipated or unanticipated or related to the intervention.

- **Submission of non-technical and technical narrative summaries of trial results**. Section 402(j) of the Act requires consideration during rulemaking as to whether non-technical and technical summaries of clinical trial results are to be required if they "can be provided in a manner that is objective and not misleading." HHS believes that further research is needed on this issue; accordingly, it is deferring the decision about whether to require narrative summaries and invites public comment.

- **Submission of the full clinical trial protocol**. The Act requires that rulemaking consider submission of the full protocol or such information "as may be necessary to help evaluate the results of the trial." In the proposed rule, HHS does not propose to require submission of the full protocol and invites public comment.

Procedures for delaying the submission of results.

Under section 402(j) of the Act, in general, results (including adverse events) must be submitted no later than one year after the earlier of the estimated or actual "*completion date*" of the trial, which is the date that the last patient visit/data collection occurs for the purpose of the primary outcome. In the proposed rule, the Responsible Party would be required to update the estimated completion date and report the actual completion date not later than 30 calendar days after the last patient visit/data collection for the purpose of the primary outcome. In the proposed rule, in general, the deadline for submitting results information would be no later than one year after this completion date, *i.e.*, the date of the last patient visit/data collection for the purpose of the primary outcome. For trials of drugs and devices not yet approved, licensed, or cleared for any use, the deadline would be the ***earlier*** of the date that is not later than one year after the completion date or the date that is 30 calendar days after FDA approves, licenses, or clears the product. These deadlines would be mandatory for all Applicable Clinical Trials unless a (1) a certification for delay is submitted or, less commonly, (2) a request for extension is submitted to the Director of NIH and granted. In all instances, clinical trial results information would be posted 30 calendar days after the date of submission of the data.

- **Submission of certification for delay.**
  - **For Applicable Clinical Trials of drugs and devices that are already approved, licensed, or cleared**, a certification for delay may be submitted via the ClinicalTrials.gov website 1 year or less after the completion date ***if*** the Responsible Party certifies that that the manufacturer of the drug or device is the sponsor of the study and the manufacturer has filed, or will file within 1 year, an application seeking approval, licensure, or clearance of a new use.
  - **For trials of drugs and devices that are not yet approved, licensed, or cleared for any use**, a certification for delay would be permitted ***if*** the certification is submitted 1 year or less after the completion date and the Responsible Party certifies that the manufacturer of the drug or device is the sponsor of the study and the manufacturer intends to continue with product development and is seeking, or may at a future date seek, initial FDA approval, licensure, or clearance of the product under study.
- **Request for extension.** The proposed rule outlines procedures for requesting that the Director of NIH grant an extension of the results submission deadline for "good cause." A single time appeals process is also proposed if the extension is not granted. The preamble notes that section 402(j) of the PHS Act does not define "good cause," and HHS identifies only two situations that might constitute "good cause": (1) the need to preserve the scientific integrity of an Applicable Clinical Trial (*e.g.*, a protocol requirement to preserve blinding for ongoing collection of data for a secondary endpoint pre-specified in the protocol following earlier data collection of the primary endpoint; or (2) emergencies, such as natural disaster catastrophes, that affect data collection at sites out of the sponsor's control. Conversely, plans for pending publication or internal delays in data analysis would not constitute "good cause" for an extension. Public comment is invited on specific situations and more general criteria that could be used to determine "good cause."
- **Two-year limitation of delay of results submission.** Clinical trial results would be required to be submitted no later than 2 years after submission of the certification for delay. (Thus, the proposed rule would allow for a maximum potential time interval of three years for submission of results after the completion date.) This maximum delay of 2 years would be applicable to all primary outcomes as well any secondary outcomes and adverse events collected by the completion date (the date the final subject was examined/data collected for the primary outcome). In contrast, because of the extraordinary and uncommon circumstances that HHS anticipates

would constitute "good cause" for a request for extension, the timeline for submission of results for an approved "good cause" extension would be at the discretion of the Director of NIH.

- In addition, the proposed rule recognizes that in some trials, data on secondary outcomes pre-specified by the protocol must be collected after the date of the final data collection for the primary outcome. The proposed rule does ***not*** permit a delay in submission of primary outcome results if some secondary outcome data must be collected later than the completion date. Instead, the proposed rule adds a new requirement that the Responsible Party submit updated data for all secondary outcomes that are measured after the completion date. Further, adverse event data must be updated, if available, each time data for a secondary outcome is submitted, and such complete secondary outcome and updated adverse event data must be submitted no later the 1 year after the date of the final visit/final data collection for the last patient.

Timely updating of information and corrections of errors (including falsified information).

- **Expansion of required 30-day updates.** The Act requires, in general, that required entries must be updated not less than once every 12 months if the information changes. It specifies only two events that require updates ***no later than 30 calendar days*** thereafter: a change in recruitment status and the occurrence of the completion date (the date of the last patient visit/data collection for the primary outcome). In contrast, the proposed rule would require an update ***no later than 30 calendar days*** after the occurrence of 11 events: (1) the study start date (the date of enrollment of the 1st subject), (2) the establishment of a non-proprietary name for the drug being studied, (3) the initiation or termination of an Expanded Access program, or assignment of the NCT number to an Expanded Access Record, (4) other changes in Expanded Access status, (5) change in overall recruitment status, including a free-text explanation of why a trial was suspended, terminated, or withdrawn (*e.g.*, safety reasons), (6) change in clinical site status (*i.e.*, the addition or removal of individual clinical trial sites), (7) change in status of IRB or other human subjects protection review board (*e.g.*, approval), (8) occurrence of the completion date, (9) change in Responsible Party, including title, (10) change in Responsible Party contact information, and (11) change in the protocol if it must be communicated to the subjects. The proposed rule would also require an update ***no later than 15 calendar days*** after a change in the status of approval, licensure, or clearance of the product under study. In addition, the "Record Verification Date" would need to be updated any time the Responsible Party reviewed and verified the accuracy of the complete set of data in the ClinicalTrials.gov entry.

- **Corrections of errors (including falsified information).** The proposed rule specifies that errors include "information that is found to be false, incorrect, inconsistent, or incomplete." In general, an error would be required to be corrected no later than 15 calendar days after the Responsible Party becomes aware or is informed by NIH of the error, whichever is earlier. However, the proposed rule makes a distinction regarding a data entry that is "falsified or based on falsified information."[5] The Responsible Party would be required to notify the Director of NIH and then either submit corrected data not later than 15 calendar days after it becomes available or notify the Director not later than 15 calendar days after determining that such information cannot be corrected or is correct as previously submitted.

IMPLICATIONS.

The proposed rule would implement major changes regarding the types of clinical trials for which submission of results data would be required, the amount and nature of required data entries for registration and submission of results, and those events for which rapid updates would be required. Manufacturers of FDA-regulated drugs and medical devices who conduct—or plan to conduct clinical trials—may wish to examine the proposed rule closely and consider submitting comments.

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King & Spalding will continue to monitor this Notice of Proposed Rulemaking. Please let us know if you would like assistance in complying with the current requirements for registration and submission of basic results, including adverse events, to ClinicalTrials.gov. We are can assist in the preparation and submission of comments regarding this NPRM.

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[1] The NPRM is available at http://ofr.gov/OFRUpload/OFRData/2014-26197_PI.pdf
[2] 42 U.S.C. 282(j).
[3] When finalized, the rule will amend Title 42 of the Code of Federal Regulations, adding new Part 11.
[4] Although the statutory deadline for implementing the "*Expanded Registry and Results Data Bank*" by rulemaking was not later than 3 years after the enactment of FDAAA (i.e., September 27, 2010), HHS did not meet this timeline.
[5] The preamble of the proposed rule refers to FDA's proposed definition of "falsification of data" to mean information that was created, altered, recorded, or omitted in such a way that the data do not represent what actually happened in the clinical trial." *See* 75 FR 7414 (Feb. 19, 2010).