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HHS Issues Final Rule that Expands the Requirements for Disclosure of Clinical Trial Data to ClinicalTrials.gov

On September 21, 2016, the Department of Health and Human Services (HHS) published a final rule¹ that greatly expands the information that sponsors of “applicable drug clinical trials” and “applicable device clinical trials” must submit to ClinicalTrials.gov for subsequent public disclosure. The new rule comes into effect on January 18, 2017 and responsible parties will have until April 18, 2017 to achieve compliance. Detailed new regulations – titled “Clinical Trials Registration and Results Information Submission” – will be codified at 42 C.F.R. Part 11. Major changes from prior law (until now existing only in statute at 42 U.S.C. § 282) include: (1) a new requirement for the submission of results and adverse events from applicable clinical trials of FDA-regulated drugs and devices not yet approved for any use; (2) expansion of the range of adverse events that must be disclosed; (3) a new requirement for the submission of study protocols and statistical plans accompanying results; and (4) clarification of the potential criminal and civil legal consequences of non-compliance. In addition, the rule sets out new requirements for all clinical trials that are funded by the National Institutes of Health (NIH).

This client alert focuses on those changes that are likely to have the greatest potential impact on pharmaceutical and medical device companies. Be aware, however, that the Final Rule is lengthy and contains additional detail.

BACKGROUND

Title VIII of the FDA Amendments Act of 2007 (FDAAA) and subsequent technical corrections in Public Law 110-316 amended section 402(j) of the Public Health Service Act (42 U.S.C. § 282(j)) by imposing new requirements for the registration of “*applicable clinical trials*” of FDA-regulated drugs (including biological products) and medical devices on the publicly accessible data bank ClinicalTrials.gov, operated by the National Library of Medicine.

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Although enforcement has been light to date, the Food and Drug Administration (FDA) has stated that it will be largely responsible for future compliance and enforcement activities related to failures to submit required information for applicable clinical trials to ClinicalTrials.gov.

- The statutory requirements for the submission of registration information took effect on December 26, 2007.
- In a phased manner, the statute required the submission of certain clinical trial results (“*basic results*”) beginning on September 27, 2008 and adverse event information beginning on September 27, 2009.
- FDAAA required HHS to consider clarification and expansion of specific requirements and to implement such changes by rulemaking. Following the issuance of a Notice of Proposed Rulemaking (NPRM)² on November 21, 2014 and the review of nearly 900 comments submitted during the public comment period, the Final Rule establishes the “Expanded Registry and Results Data Bank” specified in the statute.

The preamble to the Final Rule emphasizes that the provisions are intended to enhance patient enrollment in clinical trials, provide a mechanism to track progress of clinical trials, provide more complete results and adverse event information, and “enhance patient access to and understanding of the results of clinical trials.” Taken together, the expanded requirements will greatly increase public transparency regarding the design of clinical trials, results, and adverse events – including positive outcomes as well as negative outcomes not heretofore made public. The regulations also provide a platform for increased enforcement.

KEY PROVISIONS

CLARIFICATION OF THE DEFINITIONS OF AN “APPLICABLE CLINICAL TRIAL” AND THE RESPONSIBLE PARTY

The rule clarifies but does not change the statutory definitions of an *applicable drug clinical trial* and an *applicable device clinical trial* that must be registered on ClinicalTrials.gov, and it provides easily understood checklists. In general, these clarifications will not require pharmaceutical and medical device companies to modify their current procedures for determining which clinical investigations are in scope. However, to address the absence of a definition of “control” or “controlled” in FDAAA, the rule defines “control or controlled” very broadly to encompass all interventional studies with a pre-specified outcome measure, including single arm studies without a concurrent separate control arm. Thus, the meaning of “controlled” is much broader than the FDA evidentiary standard of “adequate and well-controlled” clinical investigations.

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The rule also clarifies, but does not change, the statutory definition of a “*responsible party*,” which is the entity that has the legal obligation to register, submit results of, and update/correct information (as needed) about applicable clinical trials. The rule states that the responsible party is the sponsor of a clinical trial, as defined in 21 C.F.R. 50.3. However, although the statute permits the sponsor to delegate responsible party obligations to the principal investigator, the rule lays out multiple characteristics of the investigator that must be met before a sponsor may do so. In addition, the rule clarifies that only one entity may be the “responsible party;” in other words, the legal obligations of the responsible party cannot be split between the trial’s sponsor and the principal investigator.

TIMELINES APPLICABLE TO SUBMISSION AND UPDATE OF REGISTRATION INFORMATION

The rule clarifies but does not modify the date when registration must occur, which is no later than 21 days after the first human subject is enrolled. The rule clarifies that, in general, “*enrolled*” means the date that the human subject or his legally authorized representative agrees to participate in a clinical trial as required in 21 C.F.R. Part 50 or 45 C.F.R. Part 46 (i.e., the date of legal informed consent).

Sponsors should be aware that the rule expands the number of data elements that must be submitted as registration information. In addition, although the rule states that, in general, registration information must be updated not less than once every 12 months, there are multiple exceptions.

- **Primary completion date.** The terms “*primary completion date*” and “*completion date*” mean the date that the final subject undergoes final data collection for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was prematurely terminated. The rule does not change the statutory requirement that responsible parties must submit the estimated primary completion date of the trial. The actual primary completion date must be submitted not later than 30 calendar days after it occurs. The precise calendar date for the actual primary completion date continues to be a critical “red flag” date for sponsors because this date directly defines the later deadline when results and adverse events must be submitted to ClinicalTrials.gov.
- **Overall recruitment status.** The “*overall recruitment status*” must continue to be updated not later than 30 calendar days after any change in overall recruitment status.
- **New updating requirements.** In addition, the rule adds multiple new requirements for update of registration entries at either 30 or 15 calendar days after changes that are not specified in the statute (e.g., intervention name must be updated to a non-proprietary name not later than 30 days after a non-proprietary name is established).³

OPENING THE CURTAIN FOR PUBLIC ACCESS TO REGISTRATION INFORMATION FOR DEVICE TRIALS

The statute specifies that HHS must “*post*” (i.e., publicly release) registration information on ClinicalTrials.gov for each applicable drug clinical trial no later than 30 days after the submission by the

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responsible party. However, for an applicable clinical trial of a device that has never been approved or cleared for any use, the statute specifies that the registration information will not be publicly released by HHS until the product is approved or cleared by FDA. The final rule explicitly allows the responsible party for an applicable trial of an unapproved or uncleared medical device to voluntarily authorize HHS to publicly post submitted registration data, which will then be released on ClinicalTrials.gov as soon as practicable. This voluntary authorization will be effected by the responsible party via a new data element in the registration module on ClinicalTrials.gov.⁴

EXPANSION OF THE REQUIREMENTS FOR SUBMISSION OF RESULTS AND ADVERSE EVENT INFORMATION

In our opinion, the most impactful new requirement in the rule is the expansion of the requirements for the submission of results and adverse event information. Prior to the rule, sponsors (i.e., responsible parties) of registered applicable clinical trials of products that had not been approved, cleared, or licensed for any use were not required to submit results or adverse events information unless the product was later authorized by FDA for marketing in the United States. Under the new rule, pharmaceutical and medical device companies will now be legally required to submit results and adverse events information from applicable clinical trials of unapproved products. One implication is that applicable clinical trials of unapproved products that yield negative results and/or adverse events information will now be disclosed in detail to the public.

In addition, the rule greatly expands the information that must be submitted for all applicable clinical trials regarding the characteristics of the human subjects, participant flow through the trial, results and adverse events. We highlight here certain major changes regarding the submission of results and adverse events:

- ***Clinical trial protocol and statistical analysis plan.*** The rule requires submission of the complete clinical trial protocol, including all amendments reviewed and approved by a human subjects protection review board (e.g., the Institutional Review Board) and the statistical analysis plan (“SAP”), if not contained in the protocol. Although certain redactions of personally identifiable information and confidential commercial information are permitted, this legal requirement will result in public disclosure – and potential scrutiny – of documents previously considered confidential and proprietary by most pharmaceutical and medical device companies.
- ***Inclusion of mortality data in all adverse event submissions.*** Prior to the rule, the statute specified that separate tables of serious adverse events and other adverse events that are not serious and exceed a frequency of 5 percent in any arm must be submitted. The rule clarifies that the numbers of subjects and the numbers at risk for such events must also be submitted. The rule continues to specify adverse “events” not “reactions,” such that the listings do not require any inference of causality or relatedness to the product. The rule also requires a listing of deaths due to any cause (i.e., all-cause mortality) with the number and frequency of deaths by arm or comparison group.

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TIMELINES FOR THE SUBMISSION OF RESULTS AND ADVERSE EVENT INFORMATION

For all applicable clinical trials initiated on or after January 18, 2017, or whose primary completion date is on or after that date, the default deadline for the submission of results and adverse events information is no later than one year after the primary completion date. There are only two processes for lawfully delaying the submission of results and adverse events information.

- ***Certification of seeking approval, licensure or clearance for a new use or certification of seeking initial approval, licensure or clearance.*** In general, before the actual primary completion date, a responsible party that is also the manufacturer and the sponsor of the applicable clinical trial that is studying a new use of a product may submit a certification that it has or will file within one year an application to FDA for approval, licensure, or clearance of the new use. Similarly, the manufacturer and sponsor of an applicable clinical trial of a drug or medical device not approved, licensed or cleared for any use may submit a certification before the actual primary completion date that it “intends to continue with product development and is either seeking, or may at a future date seek, FDA approval, licensure or clearance of the drug product (including a biological product) or a device product under study.” In both instances, the certification is submitted via ClinicalTrials.gov.
- ***Delayed submission following certification.*** Following a certification of the intent to file a marketing application for a new use within one year, the submission of results and adverse events may be delayed until 30 calendar days after the earlier of the date that FDA approves, licenses, or clears the product for the new use or issues a letter ending the regulatory review cycle without approval, licensure, or clearance for the new use, or the date that the sponsor withdraws the application without resubmission for not less than 210 calendar days. For a certification of the intent to file a marketing application for an unapproved product, the submission of results and adverse events information may be delayed until 30 calendar days after the earlier of the date that FDA approves, licenses, or clears the product for any use that was studied in the applicable clinical trial or issues a letter ending the regulatory review cycle, or the marketing application is withdrawn by the sponsor without resubmission for not less than 210 calendar days.
- ***Two-year limitation.*** Regardless of these deadlines for delayed submission with certification, the results and adverse events of all applicable clinical trials must be submitted not later than 2 years after the submission of the certification. In other words, results and adverse events must be submitted no later than three years after the primary completion date for all applicable clinical trials.
- ***Request for a “good cause” extension.*** The only other mechanism for delay in submitting the results and adverse events from an applicable clinical trial is the submission of a request for extension to the Director of NIH, including a statement of good cause and an estimated date when results and adverse

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events information would be submitted. The preamble clarifies that a “good-cause extension” will be granted only in rare and extraordinary circumstances. The rule describes the processes for appealing denial of an extension request.

VOLUNTARY SUBMISSIONS TO CLINICALTRIALS.GOV

The final rule establishes detailed disclosure requirements that apply when a responsible party *voluntarily* submits registration or results information about a clinical trial that either (1) is a trial of an FDA-regulated drug or device that does not meet the definition of an applicable clinical trial, or (2) is an applicable clinical trial that is not otherwise required to be registered (e.g., due to timing). The specific requirements vary, depending whether the initiation date and primary completion dates occur before or on/after January 18, 2017.

Importantly, the final rule interprets the underlying statutory provision, which obligates a responsible party to submit related information about *additional* clinical trials (not only the one selected for voluntary registration). If, on or after September 27, 2007, a manufacturer submits an application or premarket notification to FDA for approval, licensure, or clearance of a drug or device for the use studied in a clinical trial, the responsible party must submit registration and/or results information for *additional* clinical trials – namely, it must submit applicable clinical trials (1) that are “required to be submitted to FDA” in a premarket application or notification for the studied product and use, *and* (2) for which the manufacturer of the studied drug or device product is also the responsible party. The preamble to the final rule explains that the purpose is to avoid selective disclosure about a product on ClinicalTrials.gov.

That said, however, the requirements related to voluntary submissions remain ambiguous. It also will be important for pharmaceutical and medical device companies that are considering or that have in the past voluntarily registered or submitted results on ClinicalTrials.gov – for example, to enable publication consistent with guidelines of the International Committee of Medical Journal Editors – to conform to the new regulations and update any prior submissions as necessary.

POTENTIAL LEGAL CONSEQUENCES OF NON-COMPLIANCE

FDAAA established a variety of administrative and judicial penalties for failure to conform to ClinicalTrials.gov registration and reporting requirements. The final rule includes a regulation that expressly states non-compliance is a prohibited act that may result in civil or criminal judicial actions, as well as other penalties.

- ***Prohibited acts under the FDCA.*** Via cross-reference to the FDCA, FDAAA prohibits and penalizes actions or omissions including the failure to submit required clinical trial registration or results information; submission of false or misleading information; and the failure to submit (or to accurately submit) certifications of conformance to requirements. The preamble refers to injunctions, fines, and imprisonment as examples of enforcement consequences of violations.

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- **Civil monetary penalties.** Among available penalties, FDAAA enabled the assessment of civil money penalties, even for “unintentional” or potentially minor failures (e.g., “failure to submit [required] clinical trial information”). The express inclusion of a prohibited acts and penalties section in the regulations suggests that the government is putting companies on notice of compliance obligations and risks.
- **NIH Grant Funding.** The regulations advise that certain non-conformance may result in a loss or delay of grant funding.
- **Other Penalties.** The preamble to the final rule states the regulations should not be understood as describing the exclusive means of enforcement that the government might undertake with respect to FDAAA. Other federal laws may be invoked, such as 18 U.S.C. § 1001, which makes it a crime to make certain false statements to the government.

IMPLICATIONS FOR DRUG AND MEDICAL DEVICE COMPANIES

Because of the short timeline for ensuring compliance with the new rule (April 18, 2017), sponsors of clinical investigations should thoroughly review the requirements, implement changes in written procedures, and train personnel to ensure accurate identification of applicable clinical trials and timely submission of the expanded registration and results data to ClinicalTrials.gov. Updated procedures will also need to encompass the increase in the number of calendar date deadlines for updating certain submissions.

Counsel and compliance officers may wish to ensure that corporate leadership is aware of the new requirements for submission of results and adverse events information for all applicable clinical trials, including trials for products not approved or cleared for any use, as well as the protocol and statistical analysis plan. The public disclosure of this information, including these documents heretofore considered confidential and proprietary, has the potential to increase public scrutiny of both the conduct and outcomes of a company’s clinical trials and how a company publicly disseminates information about these trials. It may also be helpful for personnel and corporate leadership to be aware of the potential criminal and civil legal consequences of non-compliance with the rule and its expanded requirements.

King & Spalding would be pleased to assist in helping pharmaceutical and medical device companies understand and navigate the rule, update internal procedures and personnel training, and prepare short briefing materials for corporate leadership regarding major transparency changes in the requirements.

¹ 81 Fed. Reg. 22129 (September 21, 2016).

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² 79 Fed. Reg. 69566 (November 21, 2014).

³ See 42 C.F.R. 11. 64(a)(1)(i) and (iii).

⁴ The authorization by a responsible party to allow HHS to publicly post on ClinicalTrials.gov the submission of registration information for an applicable clinical trial of an unapproved or uncleared medical device will be effected through the new data element “*Post Prior to U.S. FDA Approval or Clearance.*”