On September 16, 2016, the Department of Health and Human Services (HHS) issued a final rule to expand the availability of information about applicable clinical trials provided via ClinicalTrials.gov, a publically accessible database managed by the National Library of Medicine at the National Institutes of Health (NIH). This Final Rule is indicative of a larger initiative by the current administration “to improve safety, accessibility, and impact of U.S. clinical research,” as recently discussed by U.S. Vice President, Joe Biden. The Final Rule, which takes into account hundreds of stakeholder comments received in response to a November 2014 Notice of Proposed Rulemaking (NPRM), accomplishes this goal by clarifying and expanding the submission requirements that apply to sponsors of “applicable clinical trials” regarding study design, conduct, and results, including how and when this information must be reported to ClinicalTrials.gov. In connection with the publication of the Final Rule, NIH simultaneously published a summary of the key provisions of the Final Rule including: certain definitions, registration information, results information, updates, and compliance.

By expanding the information reported and clarifying how and when data must be submitted to ClinicalTrials.gov, HHS hopes to provide public access to a standardized set of information describing the conduct and results of specified clinical trials in order to, among other things, “increase the efficiency of drug and device development processes” by enhancing the design of clinical trials, preventing duplication of unsuccessful or unsafe trials, and improving the evidence base that informs clinical care.

The requirement to submit specified information to ClinicalTrials.gov is applicable to certain clinical trials of drug products (including biological products), device products, and to pediatric postmarket surveillance studies of medical devices. Notably, the Final Rule now requires the submission of study results for completed clinical trials of products not yet approved, licensed, or cleared by the U.S. Food and Drug Administration (FDA), which was not previously required.

**Final Rule Requirements**

The Final Rule requires that the responsible party for an applicable clinical trial must register their clinical trial on ClinicalTrials.gov, and must submit results for their clinical trial in a
specified manner and format. The responsible party must also update the information provided to ClinicalTrials.gov under certain circumstances.

**Clarification of “applicable device clinical trial”**

The types of device trials considered “applicable clinical trials” has been a point of considerable confusion for medical device trial sponsors. As clarified by the Final Rule, an “applicable device clinical trial” includes:

1. pediatric postmarket surveillance of a device ordered by FDA under Section 522 of Federal Food, Drug, and Cosmetic Act (FDC Act) that is not a clinical trial;\(^5\) and
2. clinical device studies with one or more arms that meet all the following:
   a. the study is interventional;
   b. the primary purpose is not a feasibility study;
   c. the study involves a U.S. FDA-regulated device product; and
   d. one of the following applies: (i) at least one clinical site is within the United States or one of its territories; (ii) the device under investigation is a product manufactured in and exported from the United States or one of its territories for study in another country; or (iii) the clinical trial has an Investigational Device Exemption (IDE) number.

Clinical trials investigating combination products having a device primary mode of action are considered “applicable device clinical trials,” if the above definition otherwise applies.\(^6\)

**Clarification of “responsible party”**

The “responsible party,” by default, is the sponsor of the clinical trial. The sponsor of a trial is the IDE (or IND\(^5\)) holder or, for studies conducted without an IDE or IND, the sponsor is the person who initiated the trial (e.g., planned and prepared the trial) and who has authority and control over the conduct of the trial. Under the Final Rule, however, the sponsor may designate the principal investigator as the responsible party. In order to be designated as the responsible party, the principal investigator must meet all of the outlined qualification (e.g., is responsible for conducting the trial, has control over the data from the clinical trial). The criteria for determining who the sponsor is, or whether the principal investigator is qualified, is the same for applicable drug, biological, and device product clinical trials. By contrast, for pediatric device postmarket surveillance studies, the responsible party is the party ordered by FDA to conduct the study (typically the device manufacturer). The responsible party may be an organization (e.g., manufacturer, university) or an individual,\(^9\) but there may be only one responsible party per study.

**Registration Information**

The Final Rule clarifies that applicable device (and drug) clinical trials must be registered no later than 21 days after enrolling the first participant. For applicable device clinical trials, the following information must be submitted as part of the registration:\(^{10}\)
For pediatric postmarket surveillance of a device, the responsible party must submit clinical trial registration information no later than 21 days after FDA approves the postmarket surveillance plan.

Public posting of registration information\(^{11}\)

For applicable device clinical trials of a device that was previously cleared or approved by FDA, registration information submitted by the responsible party (except for some administrative information) will be posted publicly on ClinicalTrials.gov no later than 30 days after the information is submitted. For an applicable device clinical trial of a device that has not been cleared or approved by FDA, the Final Rule provides that submitted registration information generally will not be made public until the device receives clearance or approval from FDA, but no later than 30 days after the date of such approval or clearance. However, the responsible party may send written permission allowing the registration information to be made public earlier.

Results Information

The Final Rule requires a responsible party for an applicable clinical trial to submit summary results to ClinicalTrials.gov, regardless of whether the drug, biological, or device product has been approved, licensed or cleared for marketing by FDA. This represents a significant expansion of the reporting requirements, as previously, results information was only required to be submitted for applicable clinical trials once the subject device was cleared or approved by FDA.

Timeline for Reporting of Summary Results\(^{12}\)

The reporting timeline for summary results of postmarket surveillance studies (except pediatric postmarket surveillance) is one year after the primary completion date of the applicable clinical trial, and the primary completion date is the date that the final subject was examined or received an intervention for the purpose of collecting information for the primary outcome. An extension for up to two years is available if the responsible party certifies either that: (1) the product is not yet approved, licensed, or cleared for marketing and is still under development by the manufacturer; or (2) the manufacturer is the sponsor of the clinical trial and will seek approval, licensing, or clearance for marketing from FDA for the investigational product within one year. The Final Rule also allows a responsible party to request an extension for “good cause,”

- Descriptive information (e.g., study title, design, primary purpose, intervention);
- Recruitment information (e.g., eligibility, overall recruitment status);
- Location and contact information (e.g., name of sponsor, responsible party, facility information); and
- Administrative information (e.g., unique protocol identification number, IDE/IND number, human subjects protection review board status).
or a permanent waiver of the results reporting requirements for “extraordinary circumstances.”

For pediatric postmarket surveillance device studies, the responsible party must submit summary results no later than 30 days after the date on which the final report of the approved pediatric postmarket surveillance study is submitted to FDA.

Results Data to be Submitted

For the submission of summary results, the Final Rule requires that the following data be submitted in tabular form:

- participant flow;
- demographic and baseline characteristics;
- primary and secondary outcomes, including results of any scientifically appropriate statistical tests;
- administrative information, including points of contact for clinical results information and employment status of principal investigator; and
- adverse event information.

For adverse event information, tables must be submitted that include: summaries of all serious adverse events; adverse events that exceeded a frequency of 5% in any treatment arm; and all-cause mortality.

Perhaps most notably, the rule now requires the submission of the full protocol and statistical analysis plan (SAP).

For certain applicable clinical trials additional information must be submitted as outlined below:

- certain registration information must be resubmitted for an applicable device clinical trial of a device that has not been approved or cleared by FDA and for which registration information has not been made public on ClinicalTrials.gov,
- any final report that was provided to FDA for a pediatric postmarket surveillance of a device that is not a clinical trial.

Updates and other required information

While all submitted information must be updated at least once per year, certain information must be updated in a timely manner (typically within 30 days). For example, the responsible party information and overall recruitment status must be updated within 30 days of an applicable change.

Compliance and Associated Penalties

The effective date for the Final Rule is January 18, 2017, with compliance required 90 days
thereafter (April 18, 2017). Failure to comply with the Final Rule at any point after the compliance date is considered a violation of the FDC Act. Such violations may result in civil penalties including civil monetary penalties up to US$10,000 for all violations adjudicated in a single proceeding. Note, however, that if the responsible party is notified of non-compliance, and that non-compliance is not remedied within 30 days, the responsible party is subject to a penalty of up to US$10,000 for each day until the violation is corrected.15

Summary

Under the final rule, sponsors of applicable medical device clinical trials will be subject to more expansive reporting requirements. The rule clearly expands the types of clinical trials that fall under its purview, and the information required to be reported now includes information about products that have not been approved, licensed, or cleared by FDA. Given the potential for civil penalties to be imposed for failure of comply, the clarified definitions, as well as the more detailed accounting of the registration information and summary results information expected to be submitted will no doubt be welcomed by medical device trial sponsors and investigators, many of whom have struggled with the lack of clarity regarding who was responsible for compliance, whether a particular device trial was covered by the rules, and the type of information to be submitted. With compliance required by mid-April 2017, sponsors of medical device trials should closely review their current and planned trials to assess the applicability of reporting requirements that may attach under this Final Rule.

Should you have any questions about the Final Rule or achieving compliance with its requirements, please contact one of the authors of this client alert or other lawyers at Hogan Lovells with whom you work.

3 Final Rule at 1.
4 42 C.F.R. §§ 11.10 and 11.22.
For the remainder of this Update, references to pediatric postmarket surveillance of a device will assume that the study would not otherwise qualify as a clinical trial under the Final Rule.

42 C.F.R. § 11.10.

42 C.F.R. § 11.4.

“IND” means Investigational New Drug Application.


42 C.F.R. § 11.28.

42 C.F.R. § 11.35.

42 C.F.R. § 11.44.

42 C.F.R. § 11.48.

42 C.F.R. § 11.64.

42 C.F.R. § 11.66.

**Contacts**

Gerard J. Prud’homme
Partner

Jennifer Agraz Henderson
Partner

Blake E. Wilson
Senior Associate

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