

# Clinical Trials Registration and Results Information Submission; Final Rule

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Food, Drugs and Devices

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On September 21, 2016, the National Institutes of Health (NIH) published its final rule, Clinical Trials Registration and Results Information Submission, 42 C.F.R. Part 11.<sup>1</sup> Under Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA), “responsible parties” for specified clinical trials of FDA-regulated drug and device products must submit clinical trial registration information to a publicly available website at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). Responsible parties for specified clinical trials of FDA-approved drug and device products are required to submit clinical trial results information and certain adverse events information to the database as well.

FDAAA requires the Secretary of Health and Human Services (HHS) to use rulemaking to expand the requirements for submission of results information to the [ClinicalTrials.gov](http://ClinicalTrials.gov) database. It also permits the Secretary to use that rulemaking to make other changes to the data submission requirements. NIH published its proposed rule on November 21, 2014.<sup>2</sup> The final rule, released after nearly 900 comments were received, describes the expanded requirements for submitting information to [ClinicalTrials.gov](http://ClinicalTrials.gov). The regulations are effective on January 18, 2017, and responsible parties have 90 days from the effective date to come into compliance.<sup>3</sup>

The final rule makes a wide range of changes to the [ClinicalTrials.gov](http://ClinicalTrials.gov) requirements. Among the more significant of these include: (1) additional data elements for registration information submission; (2) additional data elements for results information submission; (3) a new requirement that results information be submitted for all clinical trials that are required to register, not just for approved products; and (4) more frequent data updates and corrections. These changes, along with other notable provisions, are discussed below.

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<sup>1</sup> 81 Fed. Reg. 64982 (Sep. 21, 2016).

<sup>2</sup> 79 Fed. Reg. 69566, 69577 (Nov. 21, 2014).

<sup>3</sup> NIH has also provided a summary of the rule. See Summary of HHS/NIH Initiatives to Enhance Availability of Clinical Trial Information, NIH.GOV, Sep. 16, 2016, *available at* <https://www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information>.

## Subpart A—General Provisions

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Like the FDAAA, the final rule applies to all applicable clinical trials, which are divided into “applicable device clinical trials” and “applicable drug clinical trials.” The definitions of applicable device clinical trial and applicable drug clinical trial remain largely unchanged under the final rule. The final rule specifies, however, that a clinical trial of a combination product with a device primary mode of action or a drug primary mode of action is an applicable device clinical trial or applicable drug clinical trial, respectively, as long as it meets all other criteria under the relevant definition.<sup>4</sup>

In the past, many companies have experienced significant difficulty in determining whether a given study is, or is not, an applicable drug/device clinical trial. To address this issue, the final rule establishes a method by which sponsors will be able to evaluate, based on certain registration data elements, whether a given study is an applicable clinical trial. Examples of registration elements used to determine whether a given study is an applicable clinical trial include whether the study type is “interventional;” whether, for a drug, the Study Phase is not “phase 1,” or for a device, the Primary Purpose is not “feasibility;” and whether the study involves an FDA-regulated drug or device product.<sup>5</sup>

The final rule requires submission of registration and results information by the “responsible party.” Under the final rule, the responsible party for most applicable clinical trials is either (1) the sponsor of an applicable clinical trial, or (2) a qualified principal investigator (PI) who is designated by the sponsor. To be qualified, a PI must be responsible for conducting the trial, have access to and control over data from the trial, have the right to publish trial results, and have the ability to submit and update trial information. The final rule specifies that the sponsor is responsible for ensuring that a PI who is designated as the responsible party can meet all of the above requirements. If a PI who has been designated as the responsible party can no longer meet all the above criteria, the sponsor must withdraw the PI’s designation as the responsible party. The responsible party designation then reverts back to the sponsor unless the sponsor designates a different qualified PI.<sup>6</sup> The responsible party of a pediatric postmarket surveillance of a device is the entity that FDA ordered to conduct the study. There must be only one responsible party for each study.

## Subpart B—Registration

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### Additional Data Elements for Registration Information Submission

FDAAA requires responsible parties to submit certain registration data elements to ClinicalTrials.gov. Through implementation of the database, NIH has required submission of certain other registration data elements and permitted submission of other elements. The final rule clarifies the scope and definition of existing required data elements under FDAAA and adds new required data elements.

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<sup>4</sup> 81 Fed. Reg. at 65139 (new 42 C.F.R. § 11.10, “What definitions apply to this part?”).

<sup>5</sup> *Id.* at 65143 (new 42 C.F.R. § 11.22(b), “Which applicable clinical trials must be registered?”).

<sup>6</sup> *Id.* at 65138–39 (new 42 C.F.R. § 11.4, “To whom does this part apply?”).

Under the final rule, all data elements listed in 42 C.F.R. § 11.28(a)(2) are required (if applicable) and must be submitted within 21 days of enrolling the first human subject in the trial. Examples of new data elements that are now required include: whether the study is a pediatric post-market surveillance of a device product; whether the study involves an FDA-approved drug or device product; whether, for an applicable device clinical trial of an unapproved device product, the Director is authorized to publicly post registration information that would otherwise be subject to delayed posting until the product is approved or cleared; and whether the product was manufactured in, and exported from, the U.S.<sup>7</sup>

### **Expanded Access Record**

For investigational products, FDAAA requires that the responsible party submit information regarding whether the investigational product is available through an expanded access program. NIH has interpreted this requirement as requiring responsible parties to submit an expanded access record describing how those who do not qualify for enrollment in the trial may obtain access to the investigational product.<sup>8</sup> Under the final rule, NIH has codified this requirement by making the expanded access record a specifically defined data element. Additionally, under the final rule, all trials registered to study the same investigational product will link to the same expanded access record through a shared National Clinical Trial (NCT) number. The intent is to make it easier for the public to determine whether there is expanded access to a drug and to compare different expanded access programs.<sup>9</sup>

## **Subpart C—Results Information Submission**

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### **Additional Data Elements for Results Information Submission**

FDAAA requires responsible parties to submit certain results data elements to ClinicalTrials.gov for approved products. As with registration data elements, NIH has also interpreted FDAAA as requiring submission of other results data elements for approved products and permitted submission of additional data elements. The final rule clarifies the scope and definition of existing required data elements under FDAAA and adds new required data elements. Under the final rule, all data elements in 42 C.F.R. § 11.48(a) are required (if applicable) and must be submitted within one year after the study's primary completion date, unless an extension or waiver is granted, as discussed below. Examples of new required data elements include: the overall number of units analyzed (if based on a unit other than participants), the number of baseline participants (and units); information to describe the methods for collecting adverse events; a table of all-cause mortality; and the protocol and statistical analysis plan (if not

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<sup>7</sup> *Id.* at 65144 (new 42 C.F.R. § 11.28, “What constitutes clinical trial registration information?”).

<sup>8</sup> 42 U.S.C. § 282(j)(2)(A)(ii)(II)(gg).

<sup>9</sup> 81 Fed. Reg. at 65050.

included in the protocol).<sup>10</sup> Requiring disclosure of the full protocol and statistical analysis plan marks a notable change from the proposed rule and was not mandated by FDAAA.<sup>11</sup>

### **Adverse Events Information**

Since 2009, under FDAAA, responsible parties have been required to submit information regarding (1) serious adverse events, whether anticipated or unanticipated, and (2) adverse events occurring with a frequency of greater than 5% within any arm of the clinical trial.<sup>12</sup> The final rule adds an additional element requiring responsible parties to summarize (3) all-cause mortality, with the number and frequency of deaths due to any cause by arm or comparison group.<sup>13</sup>

### **Results Information Submission Required for ALL Registered Clinical Trials, Not Just For Trials of Approved Products**

The most significant change made by the final rule is the extension of the results submission requirement to applicable clinical trials for unapproved products. FDAAA applies the results submission requirement only to clinical trials of approved products.<sup>14</sup> However, it also directs NIH to determine, through the final rule, whether the requirement should be applied to clinical trials of unapproved products.<sup>15</sup> The final rule extends the results submission requirement to studies of unapproved products.<sup>16</sup>

In the proposed rule, NIH described its rationale for extending the results submission requirement to studies of unapproved products.<sup>17</sup> The proposal states NIH's views that broader disclosure of results information about unapproved products will have public health benefits, such as mitigating information bias stemming from selective disclosure, allowing participants to make more informed decisions about volunteering to participate in clinical trials, and broadening the evidence base for systematic reviews of classes of drugs and devices.<sup>18</sup>

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<sup>10</sup> *Id.* at 65148–50 (new 42 C.F.R. § 11.48, “What constitutes clinical trial results information?”).

<sup>11</sup> *Id.* at 64999. See 42 U.S.C. § 282(j)(3)(D)(iii)(III) (providing that the final rule must require submission of “[t]he full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial”) (emphasis added).

<sup>12</sup> 42 U.S.C. § 282(j)(3)(I).

<sup>13</sup> 81 Fed. Reg. at 65149 (new 42 C.F.R. § 11.48(a)(4), “What constitutes clinical trial results information?”).

<sup>14</sup> 42 U.S.C. § 282(j)(3)(D)(ii)(I).

<sup>15</sup> *Id.* at § 282(j)(3)(D)(ii)(II).

<sup>16</sup> 81 Fed. Reg. at 65146 (new 42 C.F.R. § 11.42, “For which applicable clinical trials must clinical trial results information be submitted?”).

<sup>17</sup> 79 Fed. Reg. 69566, 69577 (Nov. 21, 2014).

<sup>18</sup> *Id.*

Under the final rule, results information must be submitted for all studies required to be registered with a primary completion date on or after January 18, 2017—regardless of whether the studied product is approved. The “primary completion date” is the date that the final subject was examined or received an intervention for purposes of collecting data for the primary outcome(s), or in the case of a pediatric postmarket surveillance, the date on which the final report is submitted to FDA.<sup>19</sup> This change is particularly significant because under the statute, sponsors were not required to submit results information for studies of investigational products until the product received FDA approval or clearance for its first indication. Thus, under certain circumstances, parties that abandoned clinical development programs were not required to submit results of clinical trials conducted under those development programs. Under the final rule, however, results submission will be required regardless of whether the sponsor chooses to submit an NDA or BLA, even if the trial proved to be unsuccessful and the development program was abandoned.

In most cases, clinical trial results must be submitted no later than one year after the primary completion date of the applicable clinical trial. However, there are two ways in which a responsible party can request an extension of the one-year results submission deadline: (1) by submitting a certification that the applicable clinical trial involves an FDA-regulated product that is either unapproved and under development, or approved but for which the sponsor is seeking approval for a new use; and (2) for “good cause.” Both exceptions are discussed in more detail below. The NIH Director may grant more than one extension for the same trial. The extension request must be submitted prior to the original deadline for submitting results information. The final rule makes clear that NIH will not grant any request for extension that is submitted after the deadline. Further, a responsible party may request a waiver of the results submission requirements; waivers are also discussed further below.

Extension of deadline by certification that the applicable clinical trial involves an FDA regulated product seeking approval

The responsible party may extend the deadline for submitting results by up to two years by submitting a certification that the applicable clinical trial studies an FDA-regulated product that is either: (1) unapproved and still under development, or (2) already approved but under study for an unapproved new use for which an application or premarket notification has been or will be filed within one year. After submission of the certification, clinical trial results need not be submitted until 30 days after the product is approved, the application or premarket notification seeking approval is withdrawn without resubmission for 210 calendar days, or, in the case of a new-use application, FDA ends the regulatory review cycle but does not approve the product, whichever occurs first. Notwithstanding the above, the deadline for results submission may be extended no longer than two years from the date the certification is submitted.<sup>20</sup>

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<sup>19</sup> 81 Fed. Reg. at 65140 (new 42 C.F.R. § 11.10, “What definitions apply to this part?”)

<sup>20</sup> *Id.* at 65146–47 (new 42 C.F.R. § 11.44(b)–(c), “When must clinical trial results information be submitted for applicable clinical trials subject to § 11.42?”).

### Extension of deadline for “good cause”

A responsible party may also request an extension for good cause. “Good cause” is not defined in FDAAA nor in the final rule. However, NIH identifies two general situations that it believes constitute good cause:

1. The need to preserve the scientific integrity of a trial; and
2. Emergencies outside the control of a responsible party that would prevent timely submission, such as natural disasters or other catastrophes.<sup>21</sup>

NIH plans to develop guidance, which will be subject to public comment, regarding what might be considered “good cause” for extension of the submission deadline. NIH also intends to post and periodically update on the ClinicalTrials.gov website a non-exhaustive list of reasons it will and will not consider to be “good cause.” Nevertheless, NIH makes clear in the preamble to the final rule that “there are likely to be only a few situations that would constitute good cause.”<sup>22</sup> In addition, NIH has specifically stated that the following two scenarios do not constitute good cause:

1. A request containing only a general statement without any specific reason for a delay in data analysis; and
2. Awaiting journal publication.<sup>23</sup>

If a request for extension for good cause is granted, the responsible party must submit clinical trial results no later than the date specified in the response granting the request. If the request is denied, the responsible party may appeal the denial.<sup>24</sup>

### Waiver

Additionally, a responsible party may request a waiver from any of the results submission requirements. The waiver request must include a description of extraordinary circumstances justifying the waiver and an explanation of why the waiver is consistent with the protection of public health or in the interest of national security. If the waiver is denied, the responsible party may appeal the denial. Like the extension request, the waiver request must be submitted prior to the original deadline for submitting results.<sup>25</sup>

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<sup>21</sup> *Id.* at 65077. *See also id.* at 65076, for a more detailed discussion of what does and does not constitute “good cause.”

<sup>22</sup> *Id.* at 65076.

<sup>23</sup> *See id.* With regard to the second scenario, NIH notes that the International Committee of Medical Journal Editors (ICMJE) stated in a proposal that “results information submission to *ClinicalTrials.gov* in compliance with [FDAAA] will not be considered ‘prior publication’ and will not preclude future publication.” *Id.* *See also* Darren B. Taichman et al., Sharing Clinical Trial Data: A Proposal from the International Committee of Medical Journal Editors, 164 ANN. INTERN. MED. 505 (2016).

<sup>24</sup> 81 Fed. Reg. at 65147 (new 42 C.F.R. § 11.44(e), “When must clinical trial results information be submitted for applicable clinical trials subject to § 11.42?”).

<sup>25</sup> *Id.* at 65150–51 (new 42 C.F.R. § 11.54, “What are the procedures for requesting and obtaining a waiver of the requirements for clinical trial results information submission?”).

## Subpart D—Additional Submission of Clinical Trial Information

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### Data Updates and Corrections

FDAAA requires responsible parties to update clinical trial registration data at least once every 12 months. Separately, it requires updates to recruitment status within 30 days after the recruitment status changes and notification to the Director within 30 days of completing an applicable clinical trial. FDAAA also states that HHS’s final regulations should establish “the appropriate timing and requirements for updates of clinical trial information, and whether and, if so, how such updates should be tracked.”<sup>26</sup>

The final rule makes several important changes to the update requirements. Under the final rule, all submitted information must be updated at least once every 12 months unless there are no changes during that period. Several other data elements require more frequent updating. For example, the primary completion date must be updated within 30 days after the clinical trial reaches its actual primary completion date, and the study completion date must be updated within 30 days after the clinical trial reaches its actual study completion date.<sup>27</sup> Additionally, the availability of expanded access must be updated within 30 days after expanded access to an investigational drug becomes available or within 30 days of a change in the type of expanded access available. The final rule also requires responsible parties to make timely corrections to errors, whether discovered by the responsible party or by the Agency during quality control review of submissions. Errors to registration information must be corrected within 15 days of discovery of the error by the responsible party or notification of the error by the Agency. Errors to results information must be corrected within 25 days of discovery of the error by the responsible party or notification of the error by the Agency.<sup>28</sup>

### Subpart E—Potential Legal Consequences of Non-compliance

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Finally, subpart E outlines potential actions—civil or criminal actions, monetary fines, and withholding of grant funding—that may be taken if responsible parties are non-compliant. The preamble to the final rule makes clear that this list is not meant to be exhaustive.<sup>29</sup>

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<sup>26</sup> 42 U.S.C. § 282(j)(3)(D)(v)(IV).

<sup>27</sup> The “study completion date” is the date that the final subject was examined or received an intervention for purposes of collecting data for primary and secondary outcome(s) as well as adverse events. 81 Fed. Reg. at 65140–41 (new 42 C.F.R. § 11.10, “What definitions apply to this part?”).

<sup>28</sup> *Id.* at 65155–56 (new 42 C.F.R. § 11.64, “When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?”).

<sup>29</sup> *Id.* at 65156–57 (new 42 C.F.R. § 11.66, “What are potential legal consequences of not complying with the requirements of this part?”).

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Drugs, and Devices practice:

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