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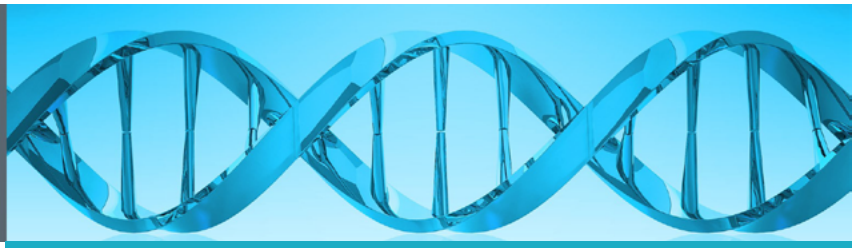

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New Clinical Trial Rule Alters Reporting Requirements

In this Issue:

New federal requirements for posting of clinical trials information address how data collected in clinical trials are submitted for public consumption. The requirements were revealed on Sept. 16 when the Department of Health and Human Services (HHS) issued a Final Rule creating new requirements for posting of clinical trials results information, which can be viewed at ClinicalTrials.gov[1].

The Final Rule intends to enhance patient enrollment, provide a mechanism to track subsequent progress of clinical trials, provide more complete results information, and enhance patient access to and understanding of the results of clinical trials.

Sponsors and sponsor-investigators of clinical trials should be aware of the following:

- Interventional clinical trials with one or more arms and one or more pre-specified outcome measures must be registered on ClinicalTrials.gov and their results information must be posted following completion of the trial.

- The sponsor of a clinical trial can delegate its duty to register and post results to a qualified Principal Investigator, who then becomes the "Responsible Party."

- Although an expanded access trial is not an "Applicable Trial" requiring registration, the Responsible Party must still submit

1 The National Institutes of Health (NIH) issued a complementary policy that extends these requirements to all clinical trials funded by NIH, regardless of whether they are subject to the Final Rule.

information about whether an unapproved drug or biologic product is available for expanded access so that information can be linked in the database.

- Results information must now be posted for drug, biologic, and device products that are not yet approved, as well as those that are approved by the Federal Food & Drug Administration (FDA), though there is the option to delay posting under certain circumstances.

- Adverse event information that is collected as part of the clinical trial protocol must now be posted as part of the results information.

- The Responsible Party is required to update the information posted at least annually.

- The Final Rule sets forth the legal consequences for failing to comply, which include civil and criminal penalties and fines, and the NIH policy states that grant funding can be withheld and non-compliance may be considered in future funding decisions.

Types of Clinical Trials Subject to the Final Rule

All interventional clinical trials with one or more arms and with one or more pre-specified outcome measures are defined as controlled clinical trials which must be registered on ClinicalTrials.gov and are considered "Applicable Clinical Trials." Certain pediatric post-market surveillance studies of devices are also considered Applicable Clinical Trials. Expanded access trials (which include widespread access under treatment protocols, intermediate-sized populations, or emergency access for individuals) are not considered Applicable Clinical Trials; however, as discussed further below, the Final Rule does require product manufacturers who are also Responsible Parties under the Final Rule to report whether expanded access is available for any Applicable Clinical Trial. In evaluating whether using a drug product in a clinical trial makes it an Applicable Clinical Trial, the sponsor should remember that the analysis is different than that determining whether an Investigational New Drug application (IND) is required to test the drug product. Even if a drug product being used in a clinical trial is IND-exempt, the trial may still be an Applicable Clinical Trial. To assist Responsible Parties in evaluating whether a trial is an Applicable Clinical Trial prior to registration, a checklist will be posted at https://prsinfo.clinicaltrials.gov prior to the Final Rule's effective date.

The Responsible Party for Posting Clinical Trial Information

The "Responsible Party" is the sponsor of the study and is responsible for registering the trial on ClinicalTrials.gov unless and until it designates a qualified Principal Investigator to fulfill the duty. Please note that the Final Rule specifies that there can be only one sponsor for a clinical trial and that sponsor is the person or entity who initiates the clinical trial. In studies where the product being studies is the subject of an IND or Investigational Device Exemption (IDE), the IND/IDE holder is the sponsor. However, in circumstances where an IND/IDE is not at issue, the analysis turns on who first initiated the study proposal. For example, the recipient of a research grant is considered the sponsor because they initiated the process by submitting a funding proposal to the funding entity. However, the funding entity of a research project who is procuring the goods or services of another entity is considered the sponsor because it initiated the process by contracting with that other entity to conduct the study subject to the funding entity's specification. When there is no external funding of a clinical trial, the person or entity who initiated the clinical trial by preparing and planning the study plan and who has appropriate authority to control and carry out the trial responsibilities is the sponsor.

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The sponsor may delegate the role of responsibly party to a Principal Investigator, but only if that Principal Investigator is responsible for conducting the trial, has access to and control over all of the data from the clinical trial, has the right to publish the result of the entire trial, and has the ability to meet all of the requirements for submission of clinical trial information. If the sponsor does not provide the Principal Investigator with the requisite information, the Principal Investigator is no longer qualified to be designated, and the responsibility reverts back to the sponsor.

Required Elements for Registration at ClinicalTrials.gov

Applicable clinical trials must be registered within 21 calendar days after the enrollment of the first human subject. Over 50 discrete data elements must be included in the registration, including items must be submitted in four categories of data elements: 1) descriptive information, 2) recruitment information, 3) location and contact information, and 4) administrative information, such as a brief title, the official title, primary purpose, number of arms, intervention names, what type of product is being studied, eligibility criteria, and name of the sponsor. A Responsible Party may delay public posting of registration information for Applicable Clinical Trials of unapproved or uncleared device products until the device product is approved or cleared or the Responsible Party can indicate to the Agency that it is authorizing the public posting of clinical trial registration information that would otherwise fall under the delay posting provision. The Final Rule encourages responsible parties to authorize such postings to increase the amount of information available to the public.

Expanded Access Records

A Responsible Party must submit information about whether expanded access to the investigational product being studied in an Applicable Drug Clinical Trial of an unapproved drug product (including an unlicensed biological product) is available.

If the Responsible Party for the Applicable Clinical Trial is both the sponsor and the manufacturer of the unapproved drug product, this rule requires the submission of a separate expanded access record containing details about how to obtain access to the investigational product. Once an expanded access record has been created for the investigational product and a National Clinical Trial (NCT) number has been assigned, the Responsible Party must update the Applicable Clinical Trial(s) with that NCT number and use that NCT number when submitting clinical trial registration information for any future Applicable Clinical Trial(s) studying the same investigational product. The NCT number allows ClinicalTrials.gov to link the existing expanded access record to the study record for the clinical trial, which provides the public with otherwise disparate information all in one location.

Results Information Posting Requirements

The Final Rule represents an expansion of the requirement for results information submission for Applicable Clinical Trials of drug, biologic, and device products to those that are approved by the FDA and now also those that are not approved, licensed, or cleared by FDA. The Final Rule requires the submission of data in a tabular format summarizing:

- participant flow
- demographic and baseline characteristics
- primary and secondary outcomes
- results of any scientifically appropriate statistical tests; and
- adverse event information

The Rule also requires the submission of the full study protocol and statistical analysis plan (if it is separate from the protocol), from which protected health information and other proprietary information may be redacted.

In general, the Rule requires submission of results information not later than 1 year after the completion date of the clinical trial, which is defined as the date the final study subject was examined or received an intervention for the purposes of collecting data from the primary and secondary outcome measures and adverse events. However, the Final Rule allows for the possibility of results posting to be delayed for up to 2 additional years from the date of submission of a certification by the Responsible Party that either (1) the unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or (2) approval will be sought within 1 year after the primary completion date of the trial for a new use of an approved, licensed, or cleared product that is being studied in the trial. Responsible parties may also request extensions to the results information submission deadlines for "good cause" as well as permanent waiver for extraordinary circumstances.

Adverse Events Information Must be Submitted

The rule requires the Responsible Party to submit information summarizing the number and frequency of adverse events experienced by clinical trial participants by arm or comparison group, as well as a brief description of each arm or group as a component of clinical trial results information. It requires submission of three tables of summarized adverse event information, including:

1. all serious adverse events;

2. other adverse events that occurred with a frequency of 5% or more in any arm of the clinical trial; and

3. all-cause mortality data by arm or group

These tables must include information about events that occurred regardless of whether they were anticipated. It also requires the Responsible Party to provide the time frame for adverse event data collection and to specify whether the collection approach was systematic or not. The Final Rule adopts the OHRP definition of an "adverse event," which the Agency states is consistent, but not identical to the FDA definition. Similarly, the definition of "serious adverse event" adopted by the Final Rule is broader than the FDA definition. However, the Final Rule is careful to say that the results information reporting requirement does not require the collection of adverse event information not specified in the protocol.

All Submitted Information Must be Updated at Least Annually

All submitted information must be updated at least annually if there are changes to report. Several of the data elements require more frequent updating to help ensure that users of ClinicalTrials.gov have access to accurate information about important aspects of an Applicable Clinical Trial. The Responsible Party must submit timely corrections to any errors discovered by the Responsible Party or the Agency during quality control review of submissions or after the information has been posted. The Responsible Party's obligation to submit updates and correction of errors ends on the date on which the required data elements for clinical trial results information have been submitted for all primary and secondary outcomes and all adverse events that were collected in accordance with the protocol, and the quality control review process has concluded.

Legal Consequences of Non-Compliance with the Final Rule and NIH Policy

The Final Rule sets forth certain legal consequences for

responsible parties who fail to comply. However, these consequences are not exclusive, so responsible parties should be aware of other federal laws that may apply. The Final Rule describes the following activities as prohibited acts that can lead to civil or criminal judicial actions against the Responsible Party:

- failure to submit a certification, or knowingly submitting a false certification, of compliance with the ClinicalTrials.gov registration requirements in connection with an FDA application for the use of a drug product or device product
- Failure to submit clinical trial information or knowingly submitting false or misleading clinical trial information

Current generally applicable fines are (1) for individuals, up to $100,000 for a misdemeanor, up to $250,000 for a felony violation and (2) for organizations, up to $200,000 for a misdemeanor, up to $500,000 for a felony violation and a civil monetary penalty of not more than $10,000 for all violations adjudicated in a single proceeding could be enforced.

In addition, if the relevant clinical trial is federally funded, grant funding can be withheld if the required reporting cannot be verified.

The NIH policy states that non-compliance will result in identification of the non-compliance in ClinicalTrials.gov and may be considered in future funding decisions.

Effective Date and Implementation

The Final Rule will be effective January 18, 2017 and Responsible Parties will have 90 calendar days after the effective date to come into compliance with its requirements. Applicable Clinical Trials of unapproved products that reach their primary completion date prior to the effective date of the rule are not subject to the rule.

For More Information

For questions regarding this information, please contact the author below, a member of Polsinelli's Health Care practice, or your Polsinelli attorney.

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