

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

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Title VIII of the Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA) expanded the legal mandate for sponsors and others responsible for certain clinical trials of FDA-regulated drug, biologic, and device products to register their studies and report summary results information to ClinicalTrials.gov,¹ which is managed by the National Library of Medicine at the National Institutes of Health (NIH). The statute expanded registration requirements and provided a legally defined timeline with specific requirements for the systematic reporting of summary trial results. Although statutory components took effect before 2010, the FDAAA directed the Department of Health and Human Services (HHS) to issue regulations regarding certain statutory provisions and to consider possible expansion of the requirements through rulemaking.

The registry currently has more than 224,000 study records, 23,000 of which display results information. Compliance with the results-reporting requirements, however, has been low across many sectors of the clinical research enterprise.² We believe this low compliance to be due, in part, to the ambiguity of some statutory requirements. The details provided in the final rule should help increase accountability within the clinical research enterprise: going forward, investigators, sponsors, and the general public will be better able to evaluate what information is required to be submitted and, in general, whether compliance has been achieved.

After issuing a Notice of Proposed Rulemaking (NPRM) in November 2014,^{3,4} HHS received nearly 900 comments from individuals and organizations, including companies, trade associations, academic institutions, patient advocacy groups, and members of the general public.⁵ After careful consideration of these comments, HHS developed the final rule, which was made publicly available on September 16, 2016. Simul-

taneously, the NIH issued a complementary final policy, under which NIH-funded awardees and investigators will be expected to submit registration and results information for all NIH-funded clinical trials, whether or not the trials are covered by the FDAAA requirements.⁶

Here, we summarize and highlight key points about the final rule (see box).

BACKGROUND

The FDAAA established legal requirements for sponsors and designated principal investigators (i.e., responsible parties) to report specified clinical trial information for certain applicable clinical trials to ClinicalTrials.gov. In addition to registration, the statute established a system and mandate for reporting summary results information within certain time frames, independent of decisions about journal publication. Under the statute, responsible parties, including, for example, grantee institutions, could be held accountable for noncompliance, with the potential for substantial civil monetary penalties, the withholding of grant funding from HHS agencies, and criminal proceedings.

The goals of the final rule are to clarify the requirements for the regulated community, interpret ambiguous key statutory provisions, and make decisions about additional reporting requirements necessary to further the goals of the statute. As a result, after a period of education and outreach to inform the regulated community of its obligations and ways of fulfilling them, the public will be better able to determine from the ClinicalTrials.gov website (<https://clinicaltrials.gov>) which trials are subject to the rule; whether and when results information is due; in general, whether there is compliance with the requirements; and whether certain enforcement actions have been taken.

Registration requirements established under

the FDAAA reflect experience with the statutory requirements in the FDA Modernization Act,⁷ as well as the International Committee of Medical Journal Editors (ICMJE) trial registration policy⁸ and other relevant U.S. and international policies.⁹ The FDAAA's registration requirements are designed to provide potential participants with information about trials of interest. The registration requirements also serve to enable funders and others to determine the need for new trials; provide a more complete listing of clinical trials to inform the medical evidence base; and enable the scientific community to examine the overall state of clinical research as a basis for engaging in quality-improvement efforts (e.g., with regard to research methods). The final rule made certain changes to the statutory requirements, as outlined in Table 1.

The FDAAA established requirements for reporting results information. No model of a structured, tabular, public database of trial-results information existed at the time. The FDAAA requirements reflect what can be considered a "minimum reporting data set" designed to provide the basic information needed to understand trial results.¹⁰ The final rule clarifies and expands the requirements for reporting results information.¹¹ Even after this expansion, however, the legal requirements represent a "floor" for reporting. Data providers can surpass these requirements by submitting results information for trials that are not covered by the statute, submitting more detailed information than required by law, and submitting information prior to the legal deadlines. In addition, ClinicalTrials.gov facilitates linking to associated journal articles for additional information.

SELECTED KEY ISSUES

The final rule provides detailed discussions of the proposals in the NPRM, relevant public comments and other considerations, and final requirements. Here we highlight issues of particular interest to readers and provide references to the final rule for additional details.

CLARIFYING STATUTORY PROVISIONS

Determination of Applicable Clinical Trial

Although the FDAAA defines "applicable clinical trial" (ACT), the regulated community could not always be certain which trials were covered because many of the statutory terms were not fully

Key Points about the Final Rule.

Clarifies the statutory language

Provides objective, structured criteria for evaluating whether a study is an "applicable clinical trial" (ACT)

Clarifies that for purposes of the final rule, all multigroup studies and all single-group interventional studies with prespecified outcome measures are considered "controlled"

Clarifies distinction between "secondary" and other prespecified outcome measures

Expands transparency beyond the basic statutory requirements

Requires submission of results information for ACTs of unapproved products

Requires submission of baseline information on race or ethnic group, if collected during the clinical trial, and other characteristics associated with primary outcome measures

Defines required levels of specification for outcome measures

Requires submission of information about adverse-event timeframe and collection method, as well as all-cause mortality

Requires submission of full protocol and statistical analysis plan at the same time as submission of results information

Other issues

NIH will post submitted records within a specified time frame, even if the records do not meet quality-control criteria; these records will include a disclaimer and, possibly, notation of the identified concerns

NIH will post registration information for trials of unapproved devices if authorized by responsible party

HHS declined requiring submission of narrative summaries

defined. The rule provides a checklist of mandatory registration data elements to allow responsible parties and members of the public to evaluate whether a study is an ACT (Table 1) (see Section IV.B.2 of the final rule).

Definition of Control or Controlled

One component of the ACT definition involves the concept of "controlled" studies. Although many sponsors are familiar with the FDA's evidentiary standard of "adequate and well-controlled" studies for drug approval, the FDAAA definition of an ACT uses the less rigorous concept of "controlled" studies. Before the final rule, "controlled" had been interpreted to include all multigroup trials without regard to the adequacy or appropriateness of the comparison groups. However, whether and which single-group interventional studies should be considered controlled for the purpose of FDAAA reporting requirements was unclear.

The NPRM explained that FDA regulations allow for both concurrent and nonconcurrent controls; the latter category includes "explicit" historical controls as well as "implicit" baseline controls. We asked for comments on evaluating which single-group studies would meet these broad criteria. We also asked for examples of single-group interventional studies that would not meet these criteria, but we did not receive

Table 1. Selected Final Rule Requirements.*

Question	Final Rule
Who is subject to the requirements?	Responsible party is considered to be the study sponsor (i.e., IND or IDE holder or the initiator of the study, considered the grantee organization for NIH-funded trials) or a sponsor-designated PI who is responsible for conducting the study, and has access to and control over the clinical data to analyze the data and publish the results
Which clinical trials are subject to the requirements?	Both registration and results information reporting required for any trial for which all of the following are true: Study type is interventional Primary purpose is NOT device feasibility Studies an FDA-regulated device product One or more of the following: At least one U.S. facility location Product manufactured in and exported from the United States Conducted under an FDA IDE OR Study type is interventional Study phase is NOT phase 1 Studies an FDA-regulated drug product (including biologic product) One or more of the following: At least one U.S. facility location Product manufactured in and exported from the United States Conducted under an FDA IND
When does information need to be submitted to or posted on ClinicalTrials.gov?	Registration Submission: Within 21 days after enrollment of the first trial participant Posting: Generally, within 30 days after submission. For ACTs of unapproved or uncleared devices, no earlier than FDA approval or clearance and not later than 30 days after FDA approval or clearance (i.e., “delayed posting”), <i>unless a responsible party authorizes posting of submitted information prior to FDA approval or clearance</i> Results information reporting Submission: Standard deadline: Within 12 months after the date of final data collection for the prespecified primary outcome measures (primary completion date) Delayed submission with certification: May be delayed for up to 2 additional years (i.e., up to 3 years total after the primary completion date) for trials certified to be undergoing commercial product development for initial FDA marketing approval or clearance or approval or clearance for a new use <i>Submitting partial results: Deadlines are established for submitting results information for a secondary outcome measure or additional adverse information that has not been collected by the primary completion date</i> Extension request: After receiving and reviewing requests, NIH may extend deadlines for “good cause” Posting: Within 30 days after submission
What information?	Registration Descriptive information about the trial: e.g., brief title, study design, primary outcome measure information, <i>studies an FDA-regulated device product, device product not approved or cleared by the FDA, post prior to FDA approval or clearance, and study completion date</i> Recruitment information: e.g., eligibility criteria, overall recruitment status, <i>why study stopped (if ended prematurely)</i> Location and contact information: e.g., name of sponsor, facility information Administrative data: e.g., secondary ID, human-subjects protection review board status Results information reporting (if collected) Participant flow: Information about the progress of participants through the trial by treatment group, including the number who started and completed the trial Demographic and baseline characteristics collected by treatment group or comparison group and for the entire population of participants in the trial, including age, sex and gender, <i>race or ethnicity, and other measures that were assessed at baseline and are used in the analysis of the primary outcome measures</i> Outcomes and statistical analyses for each primary and secondary outcome measure by treatment group or comparison group, including results of scientifically appropriate statistical analyses performed on these outcomes, if any Adverse event information: Tables of all anticipated and unanticipated serious adverse events and other adverse events that exceed a 5% frequency threshold within any group, including <i>time frame (or specific period over which adverse event information was collected), adverse-event reporting description (if the adverse-event information collected in the clinical trial is collected on the basis of a different definition of adverse event or serious adverse event from that used in the final rule), collection approach (used for adverse events during the study: systematic or nonsystematic), table with the number and frequency of deaths due to any cause by treatment group or comparison group</i> <i>Protocol and statistical analysis plan to be submitted at time of results information reporting (may optionally be submitted earlier)</i> Administrative information, including a point of contact to obtain more information about the posted summary results information

* Italics indicate requirements added by the final rule. IDE denotes Investigational Device Exemption, IND Investigational New Drug Application, and PI principal investigator.

any. HHS concluded that for purposes of this rule only, all interventional studies in humans with a prespecified outcome measure are designed to evaluate a relationship between an intervention and an outcome and therefore require a comparison that would satisfy the broader definition of “controlled.” Thus, the final rule specifies that for purposes of these requirements, all interventional studies with prespecified outcome measures, including those with one intervention group, would be considered “controlled.” It is important to note that this conclusion does not imply anything about the quality or relevance of the “control” for either single- or multigroup trials (see Section IV.A.5 of the final rule).

Definition of Secondary Outcome Measure

The rule defines a secondary outcome measure as one “that is of lesser importance than a primary outcome measure” but that is included in the statistical analysis plan (SAP) for evaluating the effect of a studied intervention. As a result, certain exploratory or other outcome measures for which there are no prespecified analytic plans are not considered “secondary outcome measures” under the rule and thus do not come under the mandatory reporting provisions. However, responsible parties may choose to provide information about exploratory, tertiary, or post hoc outcome measures (see Section IV.A.5).

EXPANDING TRANSPARENCY

Results for Trials of Unapproved Products

The regulation requires the submission of results information for ACTs regardless of the approval status of the studied products. Under the statute, submission of basic results information was required only for ACTs of products previously approved for at least one use. This expansion will advance public health benefits by ensuring that information about all ACTs will be available to inform the medical evidence base. Many benefits were noted by commenters, including that results information from trials of unapproved products could inform better assessments of risks and benefits by institutional review boards and potential future trial participants and could improve medical decision making about related marketed products (see Section III.B).

In general, parties responsible for ACTs of unapproved products must submit results information within 1 year after the primary completion date. However, the submission deadline may

be delayed for up to 2 additional years (a total of 3 years after the trial’s primary completion date) if the sponsor certifies that it intends to continue development of the drug, biologic, or device product for initial approval by the FDA (see Section IV.C.3).

Information on Baseline Characteristics

The regulation expands the requirements for submitting results information to include any baseline information on race and ethnic background that was assessed. This requirement is consistent with scientific interest in the inclusion of minorities in clinical trials and in the generalizability of research findings. In addition, the rule requires the reporting of any other measures assessed at baseline that are used in analyzing a primary outcome measure (e.g., baseline measure of blood pressure for a primary outcome measure of change in blood pressure). This requirement is designed to help ensure that results information for the primary outcome measure can be properly interpreted (see Section IV.C.4).

Specification of Outcome Measures

For each reported outcome measure submitted at registration, the rule requires the name of the specific measure (e.g., blood pressure), a description of the metric (e.g., change from baseline), and the time point or points of assessment (e.g., at 3 months) (see Section IV.B.4). As previously described, this minimum level of specificity enables readers to understand what was measured and to assess whether changes or deviations from the protocol have been made since registration.¹⁰ Additional specificity, including the method of aggregation (e.g., mean change from baseline; percent of participants with a change greater than 5 mm Hg) is required at the time of results information reporting and may be reported optionally at registration.

Information on Adverse Events

The regulation expands the pre-rule requirement for the submission of all collected information about anticipated and unanticipated adverse events in two tables: all serious adverse events and all other adverse events that exceed a threshold of 5% within a comparison group. The previously optional fields of time frame (i.e., specific period over which adverse-event information was collected) and collection approach (i.e., whether a systematic or nonsystematic method was used

to collect adverse-event information) are now mandatory under the rule. To address deficiencies in the ability to determine the total number of deaths during each trial, the regulation requires that the table of serious adverse events include the number of deaths from any cause by comparison group, if that information was collected (see Section IV.C.4).

Full Protocols and SAPs

After analyzing public comments in response to the NPRM as well as scientific discussions in the medical literature, HHS determined that having access to a copy of the full protocol and SAP is important to allow for the proper interpretation of a study's results. Therefore, the regulation requires the submission of a copy of the full protocol and SAP (if not included as part of the protocol) at the time of results information submission. These documents must include all amendments that have been approved by a human-subjects protection review board (if applicable) in a specified common electronic document format (e.g., Portable Document Format, or PDF). Although protocols and SAPs can be submitted at any time before the end of the study, an updated version would need to be submitted at the time of results information reporting. ClinicalTrials.gov will also accommodate the optional submission of informed consent forms at any time during the study life cycle (see Section III.D).

OTHER ISSUES

Posting of Submitted Information

The NIH conducts quality-control review of submitted trial information, as directed by the FDAAA. The review criteria are designed to permit detection of apparent errors, deficiencies, and inconsistencies in the submissions.¹² Examples of problems that may be identified during the review process include but are not limited to transpositions of numbers or characters; inadvertent omissions of data; and incomplete entries that are insufficient to convey their intended meaning, such as a description of an outcome measure without specification of the measurement scale being used. They also include submitted values that are obviously wrong, such as a mean age of participants of 624 years.

Our experience has shown that the quality-control review procedure helps to ensure that entries are complete and meaningful. From 2008 until publication of the final rule, the NIH did

not post any submitted information that did not fulfill the quality-control review criteria. Responsible parties received specific comments and had to address them satisfactorily prior to public posting. The rule now requires the NIH to post all submitted information on ClinicalTrials.gov within 30 days after receipt even if there are outstanding issues with the quality-control review (see Section IV.D.3). Records for ACTs that do not meet the review criteria will still be returned to the responsible party with comments. Under the new procedures, responsible parties will have 15 days to correct registration records and 25 days to correct results information records. During this process, records that still do not fulfill all quality-control review criteria 30 days after submission will be posted with a disclaimer and, possibly, a general explanation of the concerns about quality. Registry submissions will not be assigned an NCT number until the quality criteria are met. Anyone using ClinicalTrials.gov to search for studies will have an option of including or excluding records that have not met the quality-control review criteria. Once the review criteria are met, the disclaimers will be removed. Responsible parties have access to one-on-one assistance, detailed listings of quality-control review criteria, training videos, and other materials designed to facilitate record submission.

Authorizing Posting of Registry Information for Trials of Unapproved Device Products

Under the FDAAA, the NIH is prohibited from posting registration information submitted for any ACTs of a device product that has not been previously approved or cleared by the FDA. The regulation, however, specifies that the parties responsible for such trials may authorize the NIH to post registration information prior to FDA approval or clearance of the studied device product (see Section IV.B.5). Such authorization will enable interested responsible parties to follow the ICMJE and other policies that require public posting of registration information at trial initiation. To the extent that this option is chosen, the public will have greater access to information about ongoing and completed device trials.

No Requirement for Narrative Summaries

HHS is declining at this time to require narrative results summaries until further research is conducted to determine whether and, if so, how summaries can be reliably and consistently pro-

duced without being promotional or misleading. The NIH will continue to explore mechanisms for linking results information to other information that might assist users in interpreting the trial results, such as information from journal articles, publicly available FDA documents, and systematic reviews. In addition, the full protocol document will provide technical details about the trial design and analytic plan, and for a lay audience, the optional posting of informed consent forms will provide a description of the study and its anticipated benefits and risks (see Section III.C).

REGULATORY TIMELINES

The ClinicalTrials.gov data-entry system, known as the Protocol Registration and Results System (PRS), will be ready to support all regulatory submission requirements by the rule's effective date on January 18, 2017 (see Section IV.F). This interval will also provide responsible parties an opportunity to become familiar with the final rule. These parties will have an additional 90 days after the effective date (until April 18, 2017) to come into compliance with the final rule. The NIH will be providing educational materials to the regulated community at <https://prsinfo.clinicaltrials.gov>. The effective date of the final rule is key to determining the obligations of a responsible party (see Section IV.E). In general, ACTs initiated on or after the effective date must follow the requirements, as specified in the rule, for registration. ACTs that reach their primary completion date on or after the effective date must submit results information as specified in the rule. Details are available at <https://prsinfo.clinicaltrials.gov>.

DISCUSSION

The value of prospective trial registration and structured results information reporting is widely recognized.¹³⁻¹⁵ The ultimate goal of conducting human experiments is to contribute findings to the evidence base that informs future medical care. Unreported trials, or those reported in an imprecise or incomplete manner, generally have limited to no societal value. Information about trials of FDA-regulated products may be submitted with a marketing application; information about others may never be submitted to the FDA and may never be available to the public for evalu-

ation or use. For sponsors and others responsible for trials subject to the FDAAA or covered by the NIH policy, the days of deciding whether or not summary results are worth reporting are over: all such trials will have summary results information posted publicly on ClinicalTrials.gov. The time to decide whether a trial is worth doing is before the trial is started, not after participants have been put at risk.

The FDAAA and the NIH policy hold all parties responsible for clinical trials — not just the individual investigators — accountable. Many U.S. academic medical centers, including those that conduct the most clinical trials, will find that the majority of their clinical trials fall under the FDAAA, the NIH policy, or both.¹⁶ Organizations will need to ensure that their systems, procedures, and organizational values all promote complete and timely clinical trial reporting. In the end, the parties responsible for clinical trials will be held accountable by the public.¹⁷ We hope that sponsors and other relevant entities will go considerably above and beyond the minimum requirements and expectations, making an effort to honor the contributions of all study participants and ensure that others in the scientific community have access to complete and high-quality information about every clinical trial under their stewardship.

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