



Rulemaking Closes the Loop on FDAAA
801 Clinical Trial Disclosure Requirements

WHITE PAPER

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Executive Summary

The Final Rule mandates a number of changes that will impact pharmaceutical companies and the way they disclose and report data:

- The Final Rule takes effect in January 2017;
- Studies completing OR starting after January 2017 will be within scope of the new regulation;
- Results summaries for studies involving investigational products now need to be disclosed. This has a potentially large impact on companies that have no marketed products and no infrastructure to support this change in scope.
- New data elements need to be reported;
- Penalties for non-compliance are reiterated in the Final Rule, and will actually be enforced.

After years of collecting and evaluating public comments, the United States Department of Health and Human Services (HHS) has announced a final ruling on their 2014 Notice of Proposed Rulemaking (NPRM)[1] that provides clarity on the requirements for registering clinical trials and submitting results summaries of FDA-regulated drugs, biologics, and devices to ClinicalTrials.gov. The pharmaceutical industry has been waiting for this expanded rule ever since it was promised in the Food and Drug Administration Amendments Act of 2007 (FDAAA)[2].

The expansion of scope (results summarization of trials involving unapproved products) and additional reporting requirements mandated by the rule should come as no surprise, as many of the details were proposed in FDAAA and discussed in the NPRM. In addition, increased transparency has been the theme in several pieces of legislation and guidances released in recent years, including the Clinical Trials Directive[3], which requires results to be reported on the European Union Clinical Trials Register (EU CTR), and the European Medicines Association's (EMA's) policy on the publication of clinical data (Policy 0070)[4]. Both have expanded and enhanced disclosure requirements, mandating that the pharmaceutical industry share an expanded set of data in a more transparent fashion; this new ruling continues to follow this trend.

When Will This Rule Take Effect?

Compliance with rulemaking is required within 90 days of January 18, 2017, the date on which the Final Rule takes effect. Studies starting after January 18, 2017 must meet the new protocol registration requirements set out in the Final Rule, and studies with primary completion dates after this date must meet the results reporting requirements.

Which Requirements Apply: Final Rule or FDAAA 2007 Statute?

The study start date determines whether the protocol needs to be registered per requirements in the Final Rule or the FDAAA 2007 Statute.

Study Start Date	Final Rule	FDAAA 2007 Statute
On or after January 18, 2007	X	
Prior to January 18, 2007		X

The primary completion date determines whether results need to be reported per requirements in the Final Rule or the FDAAA 2007 Statute.

Primary Completion Date	Final Rule	FDAAA 2007 Statute
On or after January 18, 2007	X	
Prior to January 18, 2007		X

In a recent webinar[5], the NIH re-iterated that the study start date (protocol registration) and the study completion date (results reporting) determine which requirements must be followed, but they pointed out that these rules apply independent of when the trial was first submitted to ClinicalTrials.gov.

Recognizing that there may be some confusion regarding which requirements should be followed if a key milestone occurred before the effective date of the Final Rule and another milestone occurred after the effective date, the NIH has issued the following examples, or practical implications:

A. Study Start Date = March 2017;

Initial Registration = December 2016

- a. When first registering trial, follow the requirements in the FDAAA 2007 Statute
- b. When updating trial going forward (from January until the trial has completed), follow requirements in the Final Rule

B. Study Start Date = June 2014;

Primary Completion Date = July 2017

- c. Register trial per requirements in FDAAA 2007 Statute
- d. Report results per requirements in the Final Rule

How Have the Reporting Requirements Changed?

The Final Rule impacts some significant elements of disclosure in terms of the types of trials that are within scope of the legislation and the data-reporting requirements themselves.

Scope

The number of trials that now need to be disclosed has expanded, and more closely mirrors the types of studies that need to be disclosed to the EU CTR. Previously, trials in which investigational products were being studied were out of scope for results disclosure per FDAAA 801. However, the Final Rule now calls for results summaries to be disclosed for all applicable¹ non-Phase I trials of investigational drugs and devices with a primary completion date occurring after the Final Rule takes effect (January 18, 2017). Moreover, the Final Rule applies to both public and private sector sponsors and to other entities who meet the definition of a responsible party. The inclusion of trials involving investigational products within the scope of the Final Rule is a major change, and may impact pharmaceutical companies in the following ways:

1. Companies with no marketed drugs in their pipeline may not be familiar with the ClinicalTrials.gov reporting requirements and may not have the manpower or the expertise on staff to guide them through the disclosure process.

2. Companies who previously fiercely protected their clinical trial results (both positive and negative) until they knew in which direction their clinical program was headed may now be forced to disclose results data before they had planned to do so.

3. Companies must now develop their clinical programs and design their clinical trials with the knowledge that results data for all applicable clinical trials will be made available to the public and competitors on ClinicalTrials.gov.

In general, results summaries must be disclosed no later than 1 year after the primary completion date has occurred. However, summaries can be delayed an additional 2 years if the responsible party certifies in advance of the disclosure deadline that they will be seeking initial approval, licensure, or clearance of the investigational product. This provision has been included in the Final Rule in response to concerns that disclosing data for studies of investigational products or studies comprising a failed or abandoned program may tip a sponsor's hand, and thus put companies at a competitive disadvantage. In theory, the grace period affords 2 years of additional protection of proprietary information during which companies can make decisions regarding their clinical program.

¹The Final Rule defines an applicable clinical drug/biologic trial as one that is a controlled, clinical investigation of a product subject to FDA regulation. The Final Rule also expands the definition of an "applicable device clinical trial" to include: (a) prospective clinical studies of health outcomes comparing an intervention with a device product against a control in humans (other than small feasibility studies, or clinical trials to test prototype device products in which the primary outcome measure relates to feasibility); (b) any trial conducted to serve as pediatric post-market surveillance of a device product; and (c) any clinical trial of a combination product with a device as the primary mode of action under 21 Code of Federal Regulations (CFR) part 3.

Data Reporting Requirements

Many of the existing data fields that were defined as being optional by FDAAA 801 are now mandatory under the Final Rule. For example, race and ethnicity data of trial participants must now be reported, if collected. In addition, the full protocol, including amendments, as well as the statistical analysis plan (redaction of personally identifiable information is permitted) must be submitted at the time the results summary is disclosed.

Moreover, per the Final Rule, the protocol registrations and results summaries submitted to ClinicalTrials.gov as of January 18, 2017 will contain many fields that did not exist at all in the protocol registrations and results summaries governed by FDAAA 801. Some of these fields were added to clarify existing ambiguous elements. For example, the NIH has provided clarity surrounding the definition of an “applicable clinical trial” and has defined a “controlled” trial as an interventional trial comprised of one or more treatment arms in which one or more pre-specified outcome measures are analyzed. Additionally, the NIH has clarified the definition of a “responsible party.” To this end, a protocol summary will now need to include a checklist for evaluating which clinical trials are subject to the regulations and who is responsible for submitting required information.

Just as new data elements will be required to be reported in a protocol summary governed by the Final Rule, changes to results summaries have also been implemented. The most significant change to results summaries brought about by the Final Rule is the inclusion of mortality data associated with adverse events. This new requirement is another example of how the Final Rule mirrors the EU legislation already in effect.

Key Changes Associated with Protocol Registrations:

- A checklist for evaluating which clinical trials are subject to the regulations and who is responsible for submitting required information must be submitted
- New mandatory data fields have been added. Some of these elements were optional under FDAAA 2007 and are mandatory under the Final Rule; others are entirely new[6].
- Several data elements need to be updated more frequently than the previous standard of “every 12 months.[6]”

Key Changes Associated with Results Summaries:

- Studies involving investigational products are now in scope.
- Race and ethnicity data must be reported, if collected.
- Mortality data for each treatment arm must be reported.
- The full protocol and the Statistical Analysis Plan must be provided at the time of results disclosure.

Changes to the Timing of Reporting

After a protocol is initially registered on ClinicalTrials.gov, several data elements must be updated every 12 months. The Final Rule mandates that several of these data elements be updated as frequently as 30 days after a change has occurred, and that one device-related field be updated within 15 days of a change[6].

Furthermore, responsible parties will be required to correct or address within 15 days (for registration information) and 25 days (for results information) any errors, deficiencies, and/or inconsistencies that the NIH administrators identify in their Quality Control review process. After the QC review process has been completed, responsible parties are obligated to correct any errors uncovered during their own review.

Not only does the Final Rule outline changes to processes utilized by sponsors, it also details changes to processes used by NIH administrators themselves. The Final Rule states that administrators will be working under newly defined timelines to address quality control findings and accelerated timelines for updating certain data elements. The NIH will now be obligated to post registration information no later than 30 days after submission regardless of whether the quality control review process has been completed.

How will Compliance Be Enforced?

Although penalties for Responsible Parties who failed to comply with registration or results submission requirements were written into FDAAA 801, these penalties, in the form of civil monetary penalties and withholding of grant funds for federally funded studies, were never levied. Not only does the Final Rule outline similar potential legal consequences for non-compliance, but it adds a provision to identify “non-compliant” postings as such on ClinicalTrials.gov.

In an article published in *The New England Journal of Medicine* regarding the Final Rule, Deborah Zarin, Director of ClinicalTrials.gov, acknowledges that lack of compliance across the industry has been due, in part, to ambiguous regulations and to undefined terms within those regulations[7]. In the Final Rule, the HSH has more clearly defined terms such as “responsible party,” “applicable clinical trial,” and “controlled study”; thus, sponsors should be better equipped to determine if their trial is in scope of the new regulations put forth in the Final Rule. And, because the HHS has attempted to strip ambiguity out of the Final Rule, they will likely be far less tolerant of non-compliance with the regulations. It remains to be seen if fines will be levied; however, it is reasonable to expect that the ClinicalTrials.gov administrators will take the small step of labeling a protocol registration or results summary as “non-compliant” in the registry itself in an attempt to increase accountability and transparency.

Conclusion & Implications for Pharma

More than half of the pharmaceutical sponsors that have registered trials on ClinicalTrials.gov do not have marketed products in their pipeline and have therefore never summarized their results under FDAAA 801. Falling into compliance within 90 calendar days of the effective date of January 18, 2017 may seem like a daunting task to pharmaceutical companies and academic institutions that have no knowledge of the requirements themselves or the systems used to fulfill the requirements.

Even sponsors that are well versed in current disclosure requirements and processes may require help understanding the new regulations, assessing studies to determine how they’re affected, and/or managing the workload to remain in compliance.

What's Next?

The benefits of increased transparency are abundant. The primary purpose of the protocol registration requirements is to provide patients with information regarding clinical trials of interest. Additionally, having a publically accessible database of clinical trials enables funders to determine if additional trials need to be conducted to fill gaps in the available evidence. Furthermore, sponsors should be obligated to report both positive and negative results data so that patients, physicians, and regulators alike can make informed decisions regarding the safety and effectiveness of medicines available on the market and in clinical trial settings.

As discussed, the trend in the pharmaceutical industry is toward increased transparency and 100% compliance with regulations. Anything less than 100% compliance could (and very well should) be viewed as a deliberate lack of transparency rather than the lack of a full understanding of the regulations. Sponsors and investigators should be held accountable for this lack of compliance, and highlighting trials as being out of compliance on public registries is an important step in this process.

In a show of good faith and to demonstrate that they are being active participants in the move toward increased transparency, sponsors should consider registering and reporting results for trials not meeting the definition of an applicable clinical trial, they should consider reporting more complete summaries by completing more than just the mandatory data elements, and they should consider disclosing summaries in advance of due dates outlined in the legislation.

References

1<https://www.regulations.gov/docket?D=NIH-2011-0003>

2<http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/FoodandDrugAdministrationAmendmentsActof2007/default.htm>

3http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

4http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

5https://prsinfo.clinicaltrials.gov/webinars/finalrule/resources/Final_Rule_Webinar_One_Sept_27_2016.pdf

6<https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf>

7<http://www.nejm.org/doi/full/10.1056/NEJMSr1611785>