


Sharing is Caring: HHS Final Rule on Clinical Trials Registration and Results Information Submission

■ ■ HALL
■ ■ RENDER
KILLIAN HEATH & LYMAN



Presented by
Anne Ruff | (317)977-1450 | aruff@hallrender.com

Overview

- Prior Legislation
- NPRM and the Final Rule
- What does it require?
- Complementary NIH policy
- Considerations for Sponsors
- Contracting Considerations

Reporting Isn't New

Contents

- [1997: Congress Passes Law \(FDAMA\) Requiring Trial Registration](#)
- [2000: NIH Releases ClinicalTrials.gov Web Site](#)
- [2000–2004: FDA Issues Guidance for Industry Documents](#)
- [2004: ClinicalTrials.gov Wins the Innovations in American Government Award](#)
- [2005: International Committee of Medical Journal Editors Requires Trial Registration](#)
- [2005: State of Maine Passes Clinical Studies Registration Law \(Repealed in 2011\)](#)
- [2006: World Health Organization Establishes Trial Registration Policy](#)
- [2007: Congress Passes Law \(FDAAA\) Expanding ClinicalTrials.gov Submission Requirements](#)
- [2008: ClinicalTrials.gov Releases Results Database](#)
- [2008: Declaration of Helsinki Revision Promotes Trial Registration and Results Dissemination](#)
- [2009: Public Meeting Held at the National Institutes of Health](#)
- [2013: European Medicines Agency Expands Clinical Trial Database to Include Summary Results](#)
- [2014: Notice of Proposed Rulemaking \(NPRM\) for FDAAA 801 Issued for Public Comment](#)
- [2014: NIH Draft Policy on Registration and Results Submission of NIH-Funded Clinical Trials Issued for Public Comment](#)
- [2015: National Cancer Institute Issues Clinical Trial Access Policy](#)
- [2016: Final Rule for FDAAA 801 Issued](#)
- [2016: Final NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information Issued](#)

Reporting Isn't New

- 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.
- 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.

Why the New Rule?

The problem of undisclosed results

- An analysis of 400 clinical studies revealed that 30% had not shared results through publication or through results reporting in ClinicalTrials.gov within 4 years of completion.
- Among US-based, industry-funded phase 2 and higher clinical trials, less than 25% posted their results within a year of study completion.
- Similarly, among National Institutes of Health (NIH) funded trials, 32% remained unpublished after the median follow-up of 51 months from completion.

– Saito H, Gill CJ. How frequently do the results from completed US clinical trials enter the public domain?--A statistical analysis of the ClinicalTrials.gov database. *PLoS One*. 2014;9(7):e101826.

Why the New Rule?

- Goals are to increase generalizable knowledge
 - Improve people's ability to find clinical trials in which they may be able to participate and access investigational therapies.
 - More information about the results of trials, whether positive or negative, helps healthcare providers and patients.
 - Help researchers
 - Avoid unnecessary duplication of studies
 - Identify areas in need of study
 - Improve study designs

What the Final Rule Is and Isn't

- Tell us what you know
 - The Final Rule specifies how and when information collected in a clinical trial must be submitted to ClinicalTrials.gov.
- Not intended to dictate the science
 - The Final Rule does not specify how clinical trials should be designed or conducted, or what data must be collected.

NPRM

- Notice of Proposed Rule Making issued in November 2014
- HHS received over 900 comments from individuals and organizations
 - Companies
 - Trade associations
 - Academic institutions
 - Patient advocacy groups
 - Members of the general public



NPRM

- Things that were in the NPRM that are different in the Final Rule
 - Technical and Non-Technical Summaries were proposed but didn't make it to the Final Rule
 - Requiring submission of the protocol and SAP was not in the NPRM but did make the Final Rule
 - Guidance on redacting is still coming
 - Removed the requirement in the Final Rule that the responsible party certify submitted information is truthful, not misleading and they are aware of the potential consequences of submitting such information

Important Deadlines

- Rule Issued - September 16, 2016
- Effective Date of the Final Rule - January 18, 2017
- Compliance Date - April 18, 2017



Applicable Clinical Trial

- Interventional
- Studies a U.S. FDA regulated drug, biological or device
- Is a study other than Phase 1 drug product or device feasibility study

AND

Applicable Clinical Trial

- Any of the following apply
 - At least one study facility is located in the US or US territory
 - Study conducted under an IND or IDE
 - The study involves a drug, biological or device manufactured and exported from the U.S. or U.S. territory for study in another country

What is NOT an Applicable Clinical Trial

- Phase 1
- Device feasibility
- Non-interventional studies
- Studies taking place completely outside of the US (no US sites no US drugs/devices)
- Expanded Access

Responsible Party

- The Sponsor of the clinical trial OR
- The Principal Investigator of the clinical trial if so designated by a sponsor, grantee, contractor or awardee so long as the principal investigator is:
 - Responsible for conducting the clinical trial
 - Has access to and control over the data from the clinical trial
 - Has the right to publish the results of the trial AND
 - Has the ability to meet all of the requirements for submission of the clinical trial information

Withdrawing as Responsible Party

- If the designated PI can no longer meet the requirements, of being the responsible party, the Sponsor must withdraw the designation.
- The Sponsor will then be the responsible party until another designation is made.



Registration

- The responsible party for the applicable clinical trial is responsible for registration.
- Any applicable trial initiated after September 27, 2007 or any applicable trial that is initiated on or before September 27, 2007 and is ongoing on December 26, 2007 must be registered.
- “initiated” – the day on which the first human subject is enrolled.

Registration – What is Reported

- Applicable clinical trials initiated before January 18, 2017 follow the requirements in FDAAA.
- Applicable clinical trials initiated on or after January 18, 2017 should report based on the Final Rule:
 - Descriptive Information
 - Recruitment Information
 - Location and Contact Information
 - Administrative Data

Results – What is Reported

- Participant Flow
- Demographic and Baseline Characteristics
- Outcomes and Statistical Analyses
- Adverse Event Information
- Protocol and Statistical Analysis Plan
- Administrative Information
- Additional Clinical Trial Results Information for Applicable Device Clinical Trials of Unapproved or Uncleared Device Products



Results – When are they Reported

- If the drug or device product is approved, licensed or cleared by FDA in an applicable clinical trial:
 - Primary completion date before January 18, 2017, report in accordance with FDAAA
 - Primary completion date on or after January 18, 2017, report in accordance with Final Rule

Results – When are they Reported

- Results information must be submitted no later than 1 year after the Primary Completion Date.
- NIH Director will post results no later than 30 days after submission.
- Option for Delayed Submission:
 - new use
 - initial approval
 - extensions for good cause



Expanded Access

- Responsible parties who are both:
 - Manufacturers of an investigational drug product (including biological) that is available for expanded access use AND
 - Sponsors of an applicable clinical trial of the investigational productare required to create an expanded access record for the product.

Expanded Access

- Independent investigators are not required to do an EA record.
- The EA record is required to be submitted whether the responsible party registering the clinical trial (who is sponsor and manufacturer) oversees the availability of the product through expanded access or if someone else does.

Expanded Access

- The EA record requirements for data elements will depend on if expanded access is available for an intermediate-size population or through a treatment protocol or if expanded access is only available to individual patients.

Considerations for Drug & Device Companies

- Protecting Your Information
 - Redacting Protocols and SAPs
 - Abandoning the project
 - Delayed submission process
 - certification

Considerations for Drug & Device Companies

- Registering & Reporting Combination Products
- Voluntary Reporting
 - If you voluntarily report results that creates additional reporting obligations.

NIH Policy

- Complementary Policy issued on the same date with same effective date as Final Rule.
 - Expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results information of these trials is submitted to ClinicalTrials.gov.
- Generally consistent with the Final Rule.

NIH Policy

- Includes phase 1 clinical trials and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions.
- Applies to NIH-funded clinical trials where applications or proposals are received by NIH on or after the policy's effective date.
- Applies to NIH-conducted clinical trials initiated on or after the policy's effective date.

Penalties for Non-Compliance Final Rule and NIH Policy

Final Rule

- Civil or criminal judicial actions
- Civil monetary penalties
- Impact on funding for applicable trial funded in whole or in party by HHS

NIH

- May lead to suspension or termination of grant or contract funding
- Can be considered in future funding decisions
- Identifying clinical trial record as non-compliant in ClinicalTrials.gov

Contracting Considerations

- Sponsor's compliance with the requirements
 - Including language requiring compliance with reporting requirements
- Publication timelines based on reporting
 - Regularly Sponsors identify in CTAs the timeframe for intended joint publication or when sites can publish if there is no joint publication. Will timelines change based on public reporting

Contracting Considerations

- Delegation of responsible party designation
 - Should your PI take that on?
 - What kind of agreement will you need with Sponsor to address access and control of all the data?
 - IT considerations
 - What if there is a security issue?

Contracting Considerations

- Administrative information submission requires information about agreements between the PI and Sponsor including whether an agreement exists that restricts the PI from disclosing results after the primary completion date:
 - Final Rule permits submission of optional structured information including the restriction is for
 - less than 60 days from the date communication is submitted to Sponsor for review or
 - more than 60 but less than 180 days
- Are we making sure that our delay period is no more than 180 days? Should we push for 60?

Resources

- The Final Rule – [Here](#)
- ClinicalTrials.gov FAQs – [Here](#)
- Clinicaltrials.gov Final Rule Information Page – [Here](#)
- Final Rule Webinar Series – [Here](#)
- Applicable Clinical Trials Checklist - [Here](#)



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