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Final Rule for Section 801 of the Food and Drug Administration Amendments Act of 2007 (42 CFR Part 11)

Final Rule Webinar Series – 1 of 3
September 27, 2016

Deborah A. Zarin, Director, ClinicalTrials.gov
Rebecca J. Williams, Assistant Director, ClinicalTrials.gov
National Library of Medicine

https://ClinicalTrials.gov

Webinar Series – Overview

- Webinar #1 (September 27, 2016)
  - Overview of the Final Rule
  - Effective Date and Compliance Date
- Webinar #2 (October 5, 2016 – please register)
  - Clinical Trial Registration Information and Update Requirements
- Webinar #3 (October 11, 2016 – please register)
  - Clinical Trial Results Information and Update Requirements
  - Quality Control Review Procedures and Posting

https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar

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Administrative Information

- All telephone lines are muted
- Use the Q & A box to submit questions
  - **Ensure that "All Panelists" is selected when submitting questions**
- We will have some time for questions at the end
- We will aim to address questions not answered today in future webinars and/or with information on ClinicalTrials.gov web site
- After the webinar, please submit questions to: register@clinicaltrials.gov

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NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

- Applies to all NIH-funded awardees and investigators conducting clinical trials, funded in whole or in part by NIH
- Covers all clinical trials regardless of study phase, type of intervention, or whether subject to FDAAA
- For more information: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

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FDAAA = Food and Drug Administration Amendments Act of 2007

Today's Agenda

A. Background and final rule publication

B. Overview of key provisions in the final rule

1. Summary of key final rule provisions
2. Determination of applicable clinical trial
3. Effective date and compliance date
4. Applicability, i.e., which trials have to follow final rule requirements for registration and results submission
5. Unapproved products and results submission requirements

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Background and Final Rule Publication

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Reasons to Register Clinical Trials and Report Results

- Human Subject Protections
  - Allows potential participants to find studies
  - Assists ethical review boards and others to determine appropriateness of studies being reviewed (e.g., harms, benefits, redundancy)
  - Promote fulfillment of ethical responsibility to human volunteers – research contributes to medical knowledge
- Research Integrity
  - Facilitates tracking of protocol changes
  - Increases transparency of research enterprise
- Evidence Based Medicine
  - Facilitates tracking of studies and outcome measures
  - Allows for more complete identification of relevant studies
- Allocation of Resources
  - Promotes more efficient allocation of resources
- **THIS IS WHY STUDIES ARE CONDUCTED!**

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Paradigm Shift

- Traditionally, investigators decided whether, when and how to report results
  - Many studies never reported
  - Cherry picking of outcome measures and adverse events
- Under FDAAA and NIH policy
  - Registration and results reporting must be done on legally defined timeline
  - Organizations that sponsor studies will be held responsible
    - Requires fundamental changes throughout the CRE: funders, sponsors, investigators
- Greater transparency into human experimentation
  - The time to decide if a study is worth reporting is BEFORE the participants are put at risk, not AFTER

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CRE = clinical research enterprise

Key Clinical Trial Reporting Requirements

Reporting Requirement	ICMJE Policy (Effective in 2005)	FDAAA Final Rule (Issued in 2016)	Final NIH Policy (Issued in 2016)
Scope	Registration	Registration & Results Reporting	Registration & Results Reporting
Phase	All	Not Phase 1	All
Intervention Type	All	Drug, biologic, & device products regulated by the FDA	All (e.g., including behavioral interventions)
Funding Source	Any	Any	NIH
Enforcement	Refusal to publish	Criminal proceedings and civil penalties (up to $10,000/day); Loss of HHS funding	Loss of NIH funding

International Committee of Medical Journal Editors (ICMJE)
http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

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ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

ABSTRACT

BACKGROUND
Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA–LAMA regimen in these patients is unclear.

METHODS
We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 μg) plus the LAMA glycopyrronium (50 μg) once daily or the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) twice daily. The primary outcome was the annual rate of all COPD exacerbations.

RESULTS
A total of 1680 patients were assigned to the indacaterol–glycopyrronium group, and 1682 to the salmeterol–fluticasone group. Indacaterol–glycopyrronium showed not only noninferiority but also superiority to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol–glycopyrronium group

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Wedzicha JA, et al. *N Engl J Med*. 2016 Jun 9;374(23):2222-34.

Wedzicha et al. (2016) online at www.nejm.org

Online publication of a *N Engl J Med* original article reporting the results of the FLAME Trial (NCT01782326) explicitly linked to results information posted on ClinicalTrials.gov:

- "The protocol includes a list of 27 secondary outcome measures; we report data for 19 of these outcomes here and in Sections 4 and 5 in the Supplementary Appendix. The outcomes for which data are not reported herein can be found at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01782326)."

http://www.nejm.org/doi/full/10.1056/NEJMoa1516385#t=article

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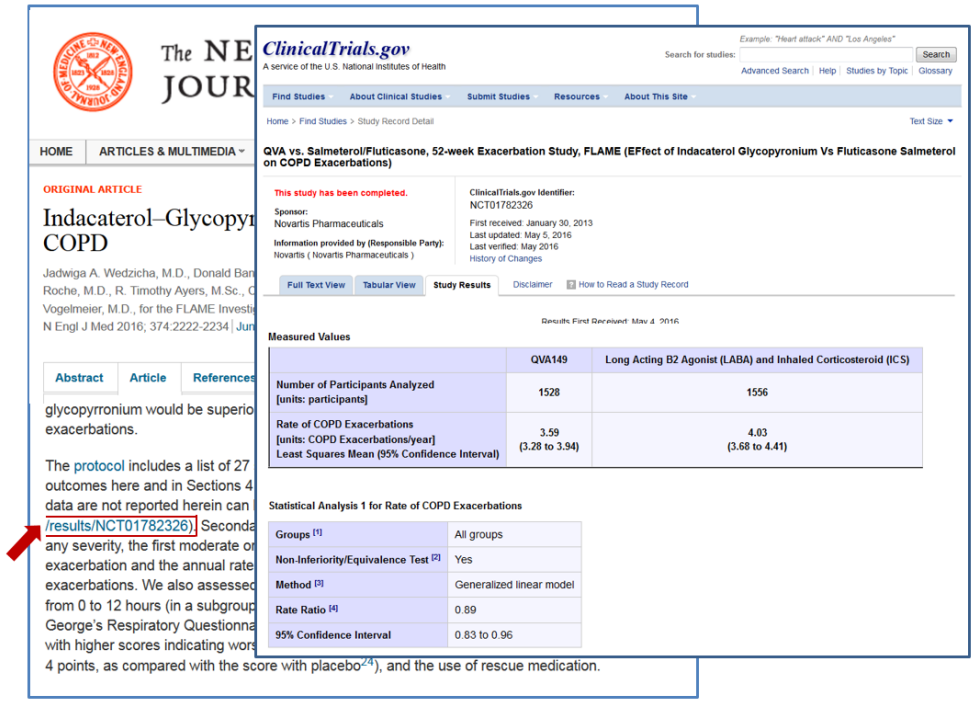

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FDAAA Time Line

- Sep 2007: FDAAA Enacted
- Dec 2007: Expanded Registration Required
- Feb 2008: NLM Board Working Group on Clinical Trials Meeting
- Sep 2008: "Basic Results" Submission Required
- Apr 2009: FDAAA Public Meeting at NIH
- Sep 2009: Adverse Events Information Required
- Nov 2014: FDAAA Notice of Proposed Rulemaking (NPRM) Issued
- Mar 2015: End of NPRM Public Comment Period
- Sep 2016: Final Rule Published

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Public Comments on NPRM

- Approximately 900 comments
  - Concerned citizens, including letter-writing campaigns
  - Scientific and professional societies
  - Patient and disease advocacy organizations
  - Medical journal editors
  - Academic institutions and medical centers
  - Drug and device manufacturers
  - Trade associations
- Final Rule preamble discusses how comments informed the rule

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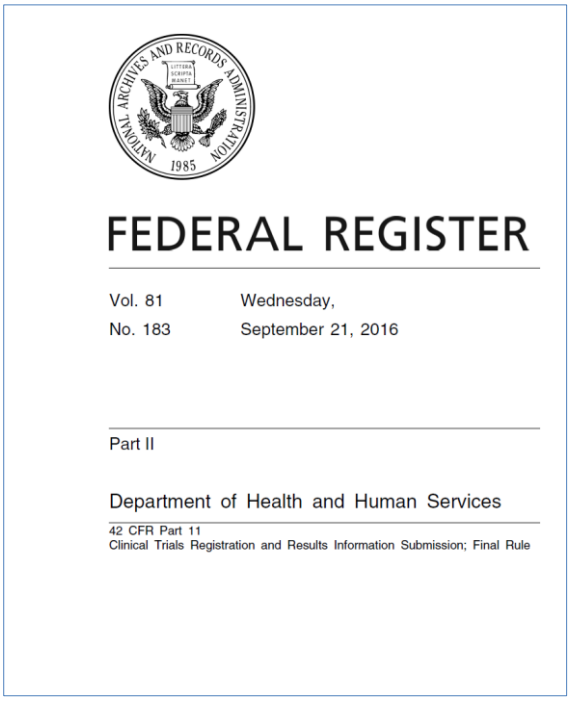

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Part II

Department of Health and Human Services

42 CFR Part 11
Clinical Trials Registration and Results Information Submission; Final Rule

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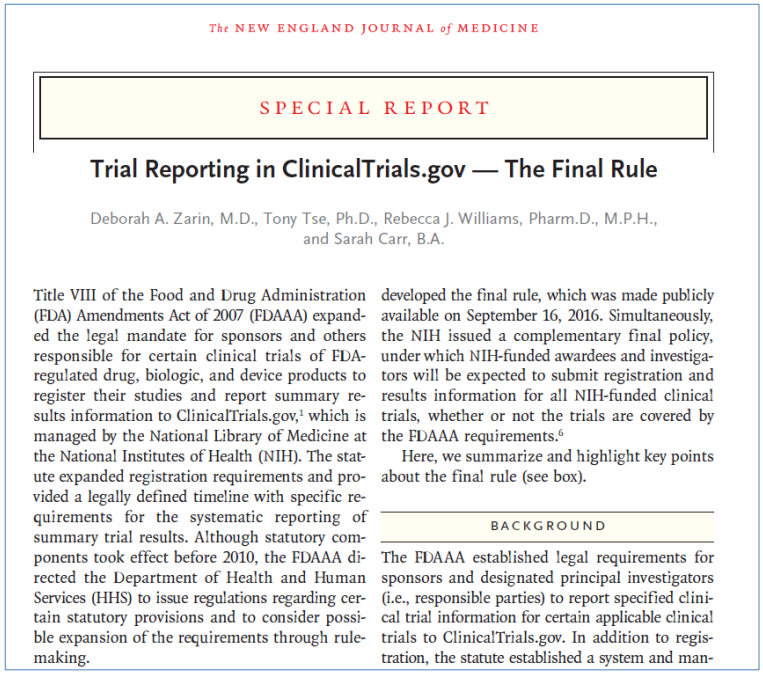

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., and Sarah Carr, B.A.

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.

developed the final rule, which was made publicly available on September 16, 2016. Simultaneously, 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 man-

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DOI:10.1056/NEJMsr1611785

Overview of Key Provisions in the Final Rule

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Summary of Key Final Rule Provisions

- Requires registration & results submission for applicable clinical trials (ACTs)
  - Allows for authorization of posting of registration information for ACTs of unapproved or uncleared device products
- Clarifies and expands registration data elements
- Expands scope of results reporting requirements to include trials of unapproved products
- Clarifies and expands results data elements
  - Requires submission of protocol (and statistical analysis plan) at time of results information submission
- Does NOT require submission of narrative summaries
- Revises Quality Control (QC) and posting process

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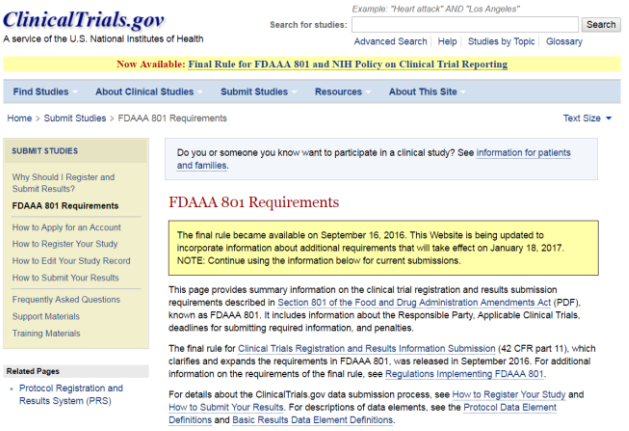
Resources about FDAAA

- See "FDAAA 801 Requirements" for more information on Section 801 of the Food and Drug Administration Amendments Act of 2007
  - https://clinicaltrials.gov/ct2/manage-recs
- See "PRSInfo" for final rule resources
  - https://prsinfo.clinicaltrials.gov



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Determination of Applicable Clinical Trial Initiated On or After January 18, 2017

- Study Type = Interventional*
- Studies a U.S. FDA Regulated Drug Product? OR Studies a U.S. FDA Regulated Device Product? = Yes [new data elements]
- Study Phase ≠ Phase 1 (drug and biological products) OR Primary Purpose ≠ Device feasibility (device products) [new menu option]
- Any of the following apply:
  - Facility Location: Country = U.S. (or U.S. territory)
  - U.S. FDA IND or IDE Number = Yes
  - Product Manufactured in and Exported from the U.S. = Yes [new element]

* 42 CFR 11.22(b); If the study is a pediatric postmarket surveillance of a device product as required by FDA under Section 522 of the Federal Food, Drug, and Cosmetic Act, it meets the definition of an applicable device clinical trial
IND = Investigational New Drug application; IDE = Investigational Device Exemption

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Definition of Controlled (42 CFR 11.10(a))

- Definition of controlled includes
  - Concurrent controls
  - Non-concurrent controls
    - Historical controls
    - Baseline as own control
- For purposes of this rule, all clinical trials with one or more arms and pre-specified outcome measure(s) are controlled

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Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10

Key Provisions of Final Rule

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Final Rule Table of Contents - Overview

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Regulatory Text - Table of Contents

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Regulatory Text - Table of Contents (cont.)

Subpart C – Results Information Submission

- § 11.40 - Who must submit clinical trial results information?
- § 11.42 - For which applicable clinical trials must clinical trial results information be submitted?
- § 11.44 - When must clinical trial results information be submitted for applicable clinical trials subject to § 11.42?
- § 11.48 - What constitutes clinical trial results information?
- § 11.52 - By when will the NIH Director post clinical trial results information submitted under § 11.48?
- § 11.54 - What are the procedures for requesting and obtaining a waiver of the requirements clinical trial results information submission?

Subpart D – Additional Submissions of Clinical Trial Information

- § 11.60 - What requirements apply to the voluntary submission of clinical trial information for clinical trials of FDA-regulated drug products (including biological products) and device products?
- § 11.62 - What requirements apply to applicable clinical trials for which submission of clinical trial information has been determined by the NIH Director to be necessary to protect the public health?
- § 11.64 - When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?

Subpart E – Potential Legal Consequences of Non-Compliance

- § 11.66 - What are potential legal consequences of not complying with the requirements of this part?

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Effective Date, Compliance Date, and Applicability

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Effective Date and Compliance Date

- Effective Date is January 18, 2017
  - Approximately 4 months after publication of the Final Rule in the Federal Register (NPRM proposed a 45-day Effective Date)
- Compliance Date is April 18, 2017 (90 days after Effective Date)
  - Responsible party has until April 18, 2017 to come into compliance with Final Rule requirements

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Final Rule, Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in This Part.

Applicability – Described in Section IV.F. (81 FR 65121)

APPLICABILITY OF REQUIREMENTS IN 42 CFR PART 11

Initiation date	Primary completion date	Registration information submission required?		Results information submission required?	
		Approved, licensed, or cleared products	Unapproved, unlicensed, or uncleared products	Approved, licensed, or cleared products	Unapproved, unlicensed, or uncleared products
On or before September 27, 2007	After December 26, 2007 and before Effective Date of Final Rule.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act.	No.
After September 27, 2007 and before the Effective Date of the Final Rule.	Before Effective Date of Final Rule.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(3)(C) and section 402(j)(3)(I) of the PHS Act.	No.
After September 27, 2007 and before Effective Date of Final Rule.	On or after Effective Date of Final Rule.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in section 402(j)(2)(A)(ii) of the PHS Act.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.
On or after Effective Date of Final Rule	On or after Effective Date of Final Rule.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.	Yes, as specified in 42 CFR part 11.

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Final Rule, Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in This Part.

Which Requirements Apply? Final Rule v. Statute

- **Registration information** determined by Study Start Date
  - Study Start Date on or after January 18, 2017: FINAL RULE
  - Study Start Date before January 18, 2017: STATUTE (FDAAA)
    - Study Start Date after September 27, 2007 but before January 18, 2017
    - Study Start Date on or before September 27, 2007, with Primary Completion Date after December 26, 2007 (i.e., ongoing study)
- **Results information** determined by Primary Completion Date
  - Primary Completion Date on or after January 18, 2017: FINAL RULE
  - Primary Completion Date before January 18, 2017: STATUTE (FDAAA)

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Final Rule, Section IV.F. Table on Applicability of Requirements in 42 CFR 11

Key Definitions

- "Study Start Date" Definition (42 CFR 11.10(b)(16))
  - Estimated date on which the clinical trial will be open for recruitment of human subjects, or
  - Actual date on which the first human subject was enrolled
- "Enroll or Enrolled" Definition (42 CFR 11.10(a))
  - A human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR Part 50 and/or 45 CFR Part 46, as applicable.
  - Potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol.

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Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10

Key Definitions

- "Primary Completion Date" (PCD) (42 CFR 11.10(a) and (b)(17))
  - Date the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome
  - If multiple primary outcome measures, the date on which data collection is completed for all of the primary outcomes
  - Estimated date updated to actual primary completion date

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Final Rule, Section IV.A.5. What definitions apply to this part? - § 11.10

Practical Implications

- Study Start Date (registration) and Primary Completion Date (results) determines which requirements apply
- Independent of when the trial is first submitted (released) to ClinicalTrials.gov
  - Ex.: Study Start Date is Mar 2017; trial first registered Dec 2016
    - Dec 2016 – follow requirements in place at time of registration (STATUTE)
    - Jan – April 2017 – update study record to meet requirements of FINAL RULE
  - Ex.: Study Start Date is Jun 2014; Primary Completion Date Jul 2017
    - Registration information follows STATUTE; results information follows FINAL RULE

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Overview of PRS Implementation Plans

- By Late November: Targeting release to Test Protocol Registration and Results System (https://prstest.nlm.nih.gov) with the registration and results final rule data elements
  - Data element definition documents and XML schema will be available
- January 18, 2017: Effective Date
  - Release will be operational on PRS; data elements newly required by the final rule will be available and have a WARNING if not completed
- April 18, 2017: Compliance Date
  - Data elements newly required by the final rule will have ERRORS if not completed (based on Study Start Date & PCD of the trial)

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Other PRS Information

- Upcoming release on PRSTest (available in PRS ~Oct 22nd) with optional data elements for submitting results information
  - Study designs in which the unit of assignment or unit of analysis is other than participants; new options for providing other units in Participant Flow and Baseline Characteristics
  - New options for specifying a number that is a "count"
  - New options for different types of "row" data
  - New "product issues" option in Organ System Class (MedDRA v. 19.0)
  - New API option for downloading information from the PRS

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Clinical Trial Results Information Deadlines

- Need to take into consideration two factors
  - Approval status of the studied drug, biological, or device product
  - Primary Completion Date

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Final Rule, Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Unapproved Products and Results Requirements

- For an applicable clinical trial (ACT) of a drug or device product that is not approved, licensed, or cleared for any use by its Primary Completion Date
- If Primary Completion Date before January 18, 2017
  - Statute applies; results submission is not required
- If Primary Completion Date on or after January 18, 2017
  - Final Rule applies; results submission is required (but delays are possible)

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Final Rule, Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in This Part.

Implications for "Certify Initial Approval"

- Certify Initial Approval submitted for an applicable clinical trial with a Primary Completion Date before January 18, 2017
  - Submission of the Certify Initial Approval is not required by the statute (FDAAA)
  - Current definition indicates that a studied product was not approved, licensed, or cleared by the FDA for any use by the PCD
  - Results are not required to be submitted (even if product approved at a later date)
  - Note: If results were submitted for such trials, not considered to be a voluntary submission under § 11.60

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Final Rule, Section IV.F. Effective Date, Compliance Date, and Applicability of Requirements in This Part.

Final Rule Results Submission Deadlines

- Primary Completion Date on or after January 18, 2017 (Final Rule)
- **Standard submission deadline**
  - Results information must be submitted no later than 1 year after the Primary Completion Date
- Delayed submission of results with certification if seeking initial approval, licensure, or clearance
  - Product not approved, licensed, or cleared by FDA for any use before the Primary Completion Date
  - Sponsor intends to continue with product development and is seeking or intends to seek FDA approval, license, or clearance

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Final Rule, Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Results Submission Deadlines – Initial Approval

- Deadline for submitting results information if delayed with certification for seeking initial approval, licensure, or clearance
  - 30 calendar days after the earlier of the date on which:
    - FDA approves, licenses, or clears the drug, biological, or device product
    - The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days
  - Two-year limitation:
    - Results information must be submitted not later than 2 years after the date on which the certification was submitted (i.e., up to 3 years after the Primary Completion Date)

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Final Rule, Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Results Submission Deadlines – New Use

- **Delayed submission** of results with certification if seeking approval, licensure, or clearance of **a new use**
  - Manufacturer is the sponsor of the ACT
  - Sponsor has filed or will file within 1 year an application or premarket notification seeking approval, licensure, or clearance of the use being studied

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Final Rule, Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Results Submission Deadlines – New Use (cont.)

- Deadline for submitting results information if delayed with certification for seeking approval, licensure, or clearance of a new use
  - 30 calendar days after the earlier of the date on which:
    - FDA approves, licenses, or clears the drug, biological, or device product
    - FDA issues a letter that ends the regulatory review cycle
    - The marketing application or premarket notification is withdrawn without resubmission for not less than 210 calendar days
  - Two-year limitation:
    - Results information must be submitted not later than 2 years after the date on which certification was submitted (i.e., up to 3 years after PCD)

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Final Rule, Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

Clarification - Initial Clearance of a Device Product

- Initial Clearance
  - Clearance of a manufacturer's original 510(k) submission for a particular device product
- Clearance of a New Use
  - Clearance of the same manufacturer's subsequent 510(k) submission for an additional use for the same device product
- Responsible parties should use their best judgment based on information available at the time to determine whether certification of initial (42 CFR 11.44(c)) or new use (11.44(b)) clearance is appropriate

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Final Rule, Section IV.C.3. When must clinical trial results information be submitted for applicable clinical trials subject to §11.42? - § 11.44

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  - Quality Control Review Procedures and Posting

https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar

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Additional Resources

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NIH Resources

- NIH News Release on the HHS Final Rule and NIH Policy
  - https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public
- NIH Policy on the Dissemination of Clinical Trial Information
  - NIH Guide Notice: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html
  - Questions: clinicaltrials.disseminationpolicy@mail.nih.gov

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ClinicalTrials.gov Resources

- Submit Studies: https://clinicaltrials.gov/ct2/manage-recs
  - FDAAA 801 Requirements – Regulations Implementing FDAAA 801
    - Changes from Current Practice Described in the Final Rule (PDF)
      - http://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf
    - Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. *N Engl J Med*; 2016. DOI: 10.1056/NEJMsr1611785.
      - http://www.nejm.org/doi/full/10.1056/NEJMsr1611785
  - Training Materials – Final Rule Webinar Series (will be archived)
- Final Rule Information: https://prsinfo.clinicaltrials.gov
- Questions: register@clinicaltrials.gov

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