ClinicalTrials.gov: Final Rule and NIH Policy - Striving for Transparency

Sarah White, MPH
Director,
Partners QI Program

Emily Ouellette, JD
Assistant Director,
Partners QI Program

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Extra! Extra!

New Requirements announced on Friday September 16, 2016:

- Final Rule (regulations (42 CFR Part 11) expands requirements under federal law FDAAA)
- New NIH Policy

Effective Date for both: January 18, 2017

Note: For Final Rule, compliance grace period until April 18, 2017

Overview

- Purpose of new requirements
- Highlights of new requirements
  - HHS Final Rule
  - NIH Policy
- Process at Partners
- Questions

Regulatory Context: Purpose of ClinicalTrials.gov

Clinicaltrials.gov

- A public federal database used to register and report results for many clinical trials.
- Created in 2000 (FDAMA) and operated by the National Library of Medicine.
- Tool used to fulfill many federal requirements as well as others (ICMJE journal requirement, CMS NCT# requirement).

Why was it created?

- Historical lack of transparency
  - not all trials are published
  - publications do not always include all pre-specified outcome measures or reflect the study design
  - unacknowledged changes are made to protocols that might affect the interpretation of the findings
- Promotes more efficient allocation of resources
- People are unable to find relevant research protocols

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

Source: Slide 8 form ClinicalTrials.gov Webinar, Overview of the Final Rule - Webinar 1 of 3, Sept. 27, 2016.

In Striving for Transparency, the New Requirements focus on:

- Expanding the scope of trials that need to register and report results
- Clarifying which studies are Applicable Clinical Trials (ACT) and need to register and report results under Final Rule
- Clarifying what information must be submitted in the database
- With clarity on requirements and enforcement timeline in place, strive to increase accountability & compliance within the clinical research enterprise

Overview of ClinicalTrials.gov modules

- Registration
  - Consists of descriptive information regarding study design, recruitment information, location and contact information and administrative data.

- Results Reporting
  - 4 Modules
    - Participant Flow
    - Baseline Characteristics
    - Outcome Measures (and Statistical Analysis)
    - Adverse Events

Who is responsible for registering the trial (Final Rule)?

- The **Responsible Party** (RP) defined as…
  - IND / IDE holder
  - If no IND/IDE:
    - "The initiator of the study"
      - The industry, cooperative group, consortium or other external sponsor that initiated the study
      - If initiated by a Principal Investigator
        - The grantee institution (e.g. BWH, MGH)
        - If no external funding, the PI
- RP can be designated to the PI

Reminder: Consequences of Non-compliance

- Final Rule*:
  - Identifying non-compliant records on ClinicalTrials.gov
  - Withholding of NIH funds
  - Monetary fines: $11,383/day/infraction

- NIH Policy:
  - Identifying non-compliant records on ClinicalTrials.gov
  - Suspension or termination of grant funding
  - Withhold future funding

*HHS has always has the authority to levy monetary fines under FDAAA, this is unchanged.

Compliance with 42 CFR Part 11 – NIH Role

- NIH will require dissemination plans (compliance with ClinicalTrials.gov registration and/or reporting requirements) in all new applications and proposals submitted after 1/18/17.
- NIH will require certification of the *grantee institution's ClinicalTrials.gov compliance* in new applications/proposals and annual Progress Reports of existing awards subject to the new policy.
- NIH will not release funding for any new clinical research awards or continuing awards if the grantee institution is not compliant with its ClinicalTrials.gov obligation.
- NIH will notify institutions of non-compliance.

Final Rule Highlights

Highlights: Final Rule

Clarification of Applicable Clinical Trials" (ACT) Definition:

Before: Definition of "Controlled" caused confusion

- Different definitions:
  - Investigators accustomed to FDA's evidentiary standard of "adequate & well-controlled". However, FDAAA used less rigorous language that could be interpreted more broadly.
    - E.g. Elaboration Document provides guidance that controlled clinical studies include not only concurrent control groups, but also non-concurrent controls such as **historical controls (e.g., literature, patient records),** validated objective outcomes using objective performance criteria (criteria based on broad sets of data from historical databases (e.g., literature or **registries**) that are generally recognized as acceptable values, or **patients as their own control**.
- Final Rule: Clarified that "controlled" = all interventional studies with pre-specified outcome measures **(including those w/ one intervention group)**

Highlights: Final Rule

<u>Additional Data Elements Required for Registration. Examples include but are not limited to:</u>

- New menu options to clarify primary purpose of the study:
  - Primary purpose of the clinical trial is NOT device feasibility
  - Primary purpose is NOT to conduct a phase one drug study

  This will help with ACT determination
- Other elements
  - Details on study design
  - If study ended prematurely, the reason why

Highlights: Final Rule

A note about registration for device studies

- Under FDAAA, NIH is prohibited to post registration information for device ACTs that have not been previously approved or cleared by the FDA. However responsible party may voluntarily elect to post registration.

Under Final Rule, Additional Data Element re: device trial:

- If FDA regulated device product
- If FDA device product not approved or cleared by the FDA
- If ok to post registration prior to FDA approval or clearance

Highlights: Final Rule

Expand the scope of ACTs that require results reporting

- Results reporting for ACTs will be required regardless of approval status of the studied products.
- Previously, results reporting required for products that were approved/cleared (for any use).

Highlights: Final Rule

Timeline for Results Reporting

- Same as now, results reporting due 1 year after the primary completion date (*the date that they final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome measure*).

Highlights: Final Rule

<u>Request for Delay in Results Reporting</u>

- 2 Year Reporting Delays Possible if file a certification:
  - "Certify New Use" - manufacturer/sponsor will file w/in 1 year or has filed marketing application for new use of approved product
  - "Certify Initial Approval" - sponsor planning on submitting marketing application for unapproved product
  - There is a **two year limitation** on the delay! (NEW)
- Extension for "good cause" an option
  - Must submit date that results will be posted
  - "Pending publication" is **<u>not</u>** considered good cause

Highlights: Final Rule

Definition of Secondary Outcome Measure

- Same as now, primary and secondary outcomes measures require results reporting
- Final Rule clarified secondary outcome measure definition:
  - "…outcome measure that is of lesser importance than a primary outcome measure" but that is included in the statistical analysis plan for evaluating the effect of a studied intervention.
  - Results due: 1 year after final subject examined or receives intervention for the purpose of final collection of data for that secondary outcome measure…

Highlights: Final Rule

Additional Results Elements Required

- Baseline characteristics
  - Same as now, age and gender information required
  - Under Final Rule, new baseline information required:
    - Race
    - ethic background (if collected) and
    - any other measures assessed at baseline and used in the analysis of the primary outcome measures

Highlights: Final Rule

Additional Results Elements Required

- Adverse Event (AE) Information
  - Information on process/method of AE collection
    - Time frame over which AEs were collected
    - Description of AE reporting method and collection approach
  - Table of number and frequency of deaths due to any cause by treatment or comparison drop

Highlights: Final Rule

<u>New uploading requirement</u>

- A copy of the protocol & statistical analysis plan will be required at some time as results posting.
- RP may redact:
  - Names/addresses/personally identifiable information
  - Trade secrets / confidential commercial information

Highlights: Final Rule

Changes re: ClinicalTrials.gov QA Review Process

- Currently, ClinicalTrials.gov did not post any submitted information that did not fulfill its quality-control review criteria.
- Under Final Rule:
  - ClinicalTrials.gov will post all submitted information on the public database no later than 30 days after receipt **even if there are outstanding quality issues**.
  - **Responsible Parties will have 15 days to correct registration records and 25 days to correct results information.**
  - Information will be posted publically with a **disclaimer** that information posted does not meet the quality control review criteria

Which requirement do I follow?

- Study Start Date (registration) and Primary Completion Date (results) determines which requirements apply
- Definitions:
  - Study start date:
    - Estimated date on which the clinical trial will be open for recruitment of human subjects, or actually date on which first human was enrolled
  - Primary Completion Date:
    - Date the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome

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

Source: Slide 29 form ClinicalTrials.gov Webinar, Overview of the Final Rule - Webinar 1 of 3, Sept. 27, 2016.

NIH Policy Highlights

Highlights: NIH Policy

Applicability of NIH Policy

- NIH policy is complementary to the Final Rule.

- All NIH defined “clinical trials” funded wholly or partially by NIH must register and post results.

- NIH “clinical trial” definition:

  “ A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”

  NIH Policy, p. 24.

Highlights: NIH Policy

Responsible Party

- The awardee and the investigator are responsible for meeting the expectations of the policy.

Effective Date

- Applies to applications for funding on or after January 18, 2017.

Partners Policy:
FDAAA Clinical Trial Registration & Results Reporting

- Policy addresses federal requirements
  - FDAAA registration and results reporting
  - CMS registration
- **Designation of an individual as Responsible Party (RP), usually the PI, to fulfill registration and results reporting requirements**
- If a PI leaves the institution:
  - Prior to leaving, PI to work with Dept./ Division Chief and QI program to 1) Identify new RP or 2) Transfer CT.gov record to new institution.
  - If PI is "lost" and CT.gov obligations *remain* at Partners institution (i.e. federal grant is/was not transferred out), Department/ Division Chief shall assume obligations or appoint new RP to meet remaining obligations.

Institutions are responsible for Investigator-initiated trials only;
Industry-sponsored trials are managed by Industry sponsor

What is currently happening at Partners?

- Summary of New Requirements posted on Research Navigator
- Address backlog of records with late results
  - Needs assessment - REDCap survey sent to all Investigators with late results (completed 11/18/16)
  - Based on need, QI will follow-up with investigators regarding action plan.
- Results Reporting Assistance: The QI Program continues to provide individual web/phone consultations.
- Educational Presentations and announcements at all Partners Institutions regarding new requirements.

What steps will be taken in the future?

- Revise eIRB module
- Include language in consent forms for NIH studies
- Work with Pre-Award re: content & placement of verification language
- Revise policy
- FAQs to be added to Research Navigator Website

Local Contacts

- Password Re-set & Registration Questions: Contact the Partners IRB Hotline (IRB@partners.org).
- Results Reporting & requirement questions. Contact the QI Program:
  - Sarah White (swhite12@partners.org)
  - Emily Ouellette (eouellette@partners.org)
  - Isabel Chico-Calero (ichicocalero@partners.org)

Resources

- Summary of Requirements on Research Navigator
- HHS News Release: Final Rule and NIH Policy: https://www.nih.gov/news-events/news-releases/hhs-take-steps-provide-more-information-about-clinical-trials-public
- ClinicalTrials.gov Final Rule Webinars 1-3: https://clinicaltrials.gov/ct2/manage-recs/present#FinalRuleWebinar

Questions?

Current Requirements
(for context if needed)

	FDAAA – a law	ICMJE - voluntary
What to register	Interventional trials: drugs, biologics, devices Phase 2 – 4 US FDA jurisdiction (e.g IND/IDE or US site)	Any human research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.
When to Register	At trial initiation: not later than 21 days of enrollment of 1st subject Update at least every 12 months	Prior to enrollment of 1st subject
Results reporting	"Applicable Clinical Trials" using FDA approved or cleared (for any use) products.	NO
If non-compliant	Public notice; NIH funds withheld; FDA sanctions, civil monetary penalties (up to $10, 000/day)	Cannot publish in select journals

	CMS
What to register	'Qualifying Clinical Trials' as determined by Medicare Coverage Analysis (MCA) *Note – CMS requirements are independent of FDAAA*
When to Register	Prior to first subject being enrolled
Results reporting	NO
If non-compliant	CMS will not accept billing claims for items and services provided