ClinicalTrials.gov Registration and Reporting

NIH Collaboratory Kick Off Meeting – November 19, 2019

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Topics

• Recent Regulatory Changes
• PRS Database Results Reporting Overview
• Issues Related to Reporting of Pragmatic CRTs
• Development of CRT Proto-paper and Supplementary Materials
Recent Regulatory Changes
Why Register and Report Results?

• Required by medical journals
  • Registration for all clinical trials (all interventions)

• Federal regulations (42 CFR Part 11: “Final Rule”)
  • Registration & results information submission for “applicable clinical trials”
  • Federal law (FDAAA 801): in effect since 2007; regulations: effective since January 18, 2017; compliance date: April 18, 2017

• Expectation for NIH-supported trials
  • Registration & results submission, even if not subject to 42 CFR Part 11
  • Policy effective: January 18, 2017

Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11)
FDAAA 801 = Section 801 of the Food and Drug Administration Amendments Act of 2007
General Requirements: Final Rule

The **Responsible Party** for an **Applicable Clinical Trial (ACT)** must:

1. **Register** the ACT in ClinicalTrials.gov no later than 21 days after enrollment of the first participant.

2. **Update** the ACT in ClinicalTrials.gov at least once every 12 months (some information within 15 or 30 days of change**).

3. **Submit summary results** (including adverse events) for certain ACTs not later than 1 year after the trial’s **Primary Completion Date**
   - Delays allowed in some circumstances


** Update requirements described in 42 CFR 11.64
General Requirements - NIH Policy

• All NIH-funded clinical trials (not just “applicable clinical trials”)
  • Applies to applications for funding submitted on or after January 18, 2017 for clinical trials initiated on or after January 18, 2017

• “For those covered by the NIH policy only, NIH-funded awardees and investigators will be expected to submit the same registration and results information in the same timeframes as those subject to the statute and rule”

PRS Database Results Reporting
Overview
Results Database Objectives

• Satisfy legal requirements
• Promote objective, standardized reporting
• Facilitate “good reporting practices”, including publishing (CONSORT) and regulatory guidelines
• Provide structured data entry to ensure complete reporting, efficient quality review, and consistent display of data elements
• Support detailed searches with the use of database structure and other NLM functions

Adapted from Table 2 in Zarin DA et al. N Engl J Med 2011;852-60.
Clarifications about Results Reporting Requirements

• Does NOT prescribe how study should be conducted

• Summary results at the end of the trial
  • No interim or “real time” reporting; no participant level reporting

• Information currently targeted at readers of the medical literature
  • “Tables” of information/“just the facts”; no conclusions or discussion

• Results submission is not required for registered studies that are not subject to 42 CFR Part 11 or NIH Policy
  • For example, if not studying an FDA-regulated product and no NIH funding
  • Although other funding policy might require results submission
Registration, Results Submission and Publication

• Deadline for submitting results to ClinicalTrials.gov is independent of publication status

• Submitting results to ClinicalTrials.gov will not interfere with publication*
  • Failure to register WILL interfere with publication!

• ClinicalTrials.gov records are linked, via NCT number, to publications
  • Ensure the registration record is up-to-date

A total of 27 secondary outcome measures were prespecified in the protocol; we report data for 21 of these outcomes in this article and in the Supplementary Appendix. The data and status for all primary and secondary outcomes are available at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/results/NC01097694).
Results Information

- Participant Flow
- Baseline and Demographic Characteristics
- Primary and Secondary Outcomes
  - Scientifically appropriate tests of statistical significance
- Adverse Event Information
- Protocol and Statistical Analysis Plan (if PCD on or after Jan 18, 2017)
- Informed Consent Form (Revised Common Rule)
- Administrative Information
  - Point of Contact (for scientific information)
  - Certain Agreements (restrictions on PI to discuss or publish results)

Study Documents

• Full Protocol and Statistical Analysis Plan (SAP) required with results information if Primary Completion Date is on or after January 18, 2017

• Informed Consent Form optional (81 FR 64999)
  • BUT, new Common Rule requires informed consent form posting

https://clinicaltrials.gov/ct2/show/NCT02862600
Protocol and Statistical Analysis Plan

• A copy of the protocol and statistical analysis plan (if not included in protocol)
  • Including all amendments approved by human subjects review board (if applicable) before time of submission that apply to all locations
  • Cover page with Official Title, NCT number, and date of document
  • May redact:
    • Names, addresses, and other personally identifiable information
    • Trade secret and/or confidential commercial information (unless otherwise required to be submitted under this part)
  • Portable Document Format Archival (PDF/A)
  • Will be posted on ClinicalTrials.gov (made public)
  • Must be in English

Final Rule Section III.D. Submission of Protocols and Statistical Analysis Plans
(81 FR 64999 - 65002)
Informed Consent Form
Revised Common Rule (45 CFR 46.116(h))

• The revised Common Rule requires that for any clinical trial conducted or supported by a Common Rule department or agency, one consent form be posted on a publicly available federal website within a specific time frame.

• Federal websites that may be used to satisfy the requirement:
  • ClinicalTrials.gov (for registered clinical trials)
  • Regulations.gov (Docket ID: HHS-OPHS-2018-0021)

• HHS and others are developing instructions and other materials providing more information about this posting requirement.

• The compliance date for this provision is January 21, 2019.

Current: Results information submission

1. Sponsor Account
   - Update study record

2. Registration Information
   - Results Information
   - Automated Validation
   - Address QC Review Issues
   - QC Review Comments

3. Submit study record
   - QC Review Staff
     - Manual Validation
     - Quality Control Review
     - No “Major” Issues
     - “Major” Issues

4. Backend Processing
   - Public Posting
Final Rule: Posting and Quality Control

• 42 CFR 11.52: By when will the NIH Director post submitted clinical trial results information?
  • “… will post publicly clinical trial results information on ClinicalTrials.gov not later than 30 calendar days after the date of submission.”

• 42 CFR 11.64(b): When must clinical trial information submitted to ClinicalTrials.gov be updated or corrected?
  • Director may provide electronic notification to the responsible party of apparent errors, deficiencies, and/or inconsistencies that are identified by established quality control review procedures
  • The responsible party must correct or address all apparent errors, deficiencies, and/or inconsistencies in clinical trial results information not later than 25 calendar days after the date of electronic notification
Posting Results Within 30 Days

• Will post study record with results information following each QC review

• If QC review process has not concluded, include two types of information:
  1. General notice that QC review process has not concluded
  2. Brief, standard QC review comment (“major” issue) identifying relevant section and data element

• Responsible party will continue to receive in the PRS the QC review comments with additional details about the “major” issue and any “advisory” issues

• Will post all versions of QC reviewed record until process concludes (no “major” issues)

• Archive site will provide access to all posted versions (History of Changes), including those with QC review issues, consistent with current practices
Future: Results information submission

1. Sponsor Account
2. Registration Information
   - Automated Validation
   - Results Information
   - Address QC Review Issues
3. QC Review Staff
   - Manual Validation
   - Quality Control Review
4. Public Posting
   - General Notice and Standard QC Review Comments

Submit study record
Update study record
QC Review Comments
Scope: Posting Results Within 30 Days

• Will apply to the following applicable clinical trials (ACTs) submitted with results information:
  • Study Start Date on or after January 18, 2017 (Final Rule Effective Date); AND
  • Results information first submitted after implementation date (estimate January 2020)

For more information, see the “Updated Quality Control and Posting Procedures Webinar” section on the Training Materials page*

* https://clinicaltrials.gov/ct2/manage-recs/present#QCPostingWebinar
Issues Related to Reporting of Pragmatic CRTs to ClinicalTrials.gov
Issues Noted in Conversation with the NIH Collaboratory

• “If you’ve seen one embedded pragmatic CRT, you’ve seen one” – trials are unique, therefore development of broadly applicable guidance is challenging

• How should enrollment be represented, and what determines the Study Start Date?
  • Cluster units join the trial before the first participant, engage in run-in prior to accrual
  • Participants are often not required to sign informed consent (interventions of limited risk)

• How should the Primary Completion Date be defined?
  • Participant data collected via state or CMS health care services are not available for analysis until 18 months have passed (3-6 months for claims processing, 1 year for creation and cleaning of analytic variables)
Issues Noted in Conversation with the NIH Collaboratory

• To ensure consistent reporting, are there tools or resources in addition to those in development for PI’s to use as they prepare to report results? Yes!

  • Results submission 1-on-1 assistance – contact us! Email register@clinicaltrials.gov to schedule a teleconference
  • PRS Guided Tutorials (BETA)
  • Results Templates and Checklists
  • ClinicalTrials.gov Results Review Criteria
  • Proto-paper (like 5 existing study designs) in development
Development of CRT Proto-paper and Supplementary Materials
CRT Fictional Manuscript, Example Study Entry, and Supplementary Materials

• Fictional Manuscript:
  • Describes analyses at the participant level
  • Follows CONSORT recommendation to include an ICC for the Primary Outcome Measure assessment

• Example study entry:
  • Exemplifies inclusion of participants and units (clusters) in a single study record
  • Demonstrates reporting of pre-specified adverse events

• Supplementary materials:
  • Will be designed to address issues not covered in chosen example
ClinicalTrials.gov Final Rule Resources

• Final Rule Information Page: https://prsinfo.clinicaltrials.gov
  • Final Rule Webinar Series
  • Applicable Clinical Trial Checklist and Elaboration (ACT Checklist)
  • Frequently Asked Questions
  • Data Element Definitions
  • PRS User’s Guide
Additional Resources

International Committee of Medical Journal Editors (ICMJE) Policy

HHS Final Rule Clinical Trials Registration and Results Information Submission
  https://www.federalregister.gov/d/2016-22129

NIH Policy on the Dissemination of Clinical Trial Information

National Cancer Institute (NCI) Policy Ensuring Public Availability of Results from NCI-supported Clinical Trials
Additional Resources (cont.)

ClinicalTrials.gov Information (Submit Studies page)
https://clinicaltrials.gov/ct2/manage-recs

Office of Extramural Research (OER)
https://grants.nih.gov/policy/clinical-trials.htm

Food and Drug Administration (FDA)
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm
Select Publications

Available at: http://www.clinicaltrials.gov/ct2/resources/pubs


Thank you

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