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ClinicalTrials.gov Registration and Reporting

NIH Collaboratory Kick Off Meeting – November 19, 2019

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National Center for Biotechnology Information

https://ClinicalTrials.gov

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)
    - http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

- **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

CODE OF FEDERAL REGULATIONS

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

NIH National Institutes of Health
Turning Discovery Into Health

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

** Full definition in 42 CFR 11.10; see ACT Checklist and Elaboration, https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf*

*** 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”

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

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

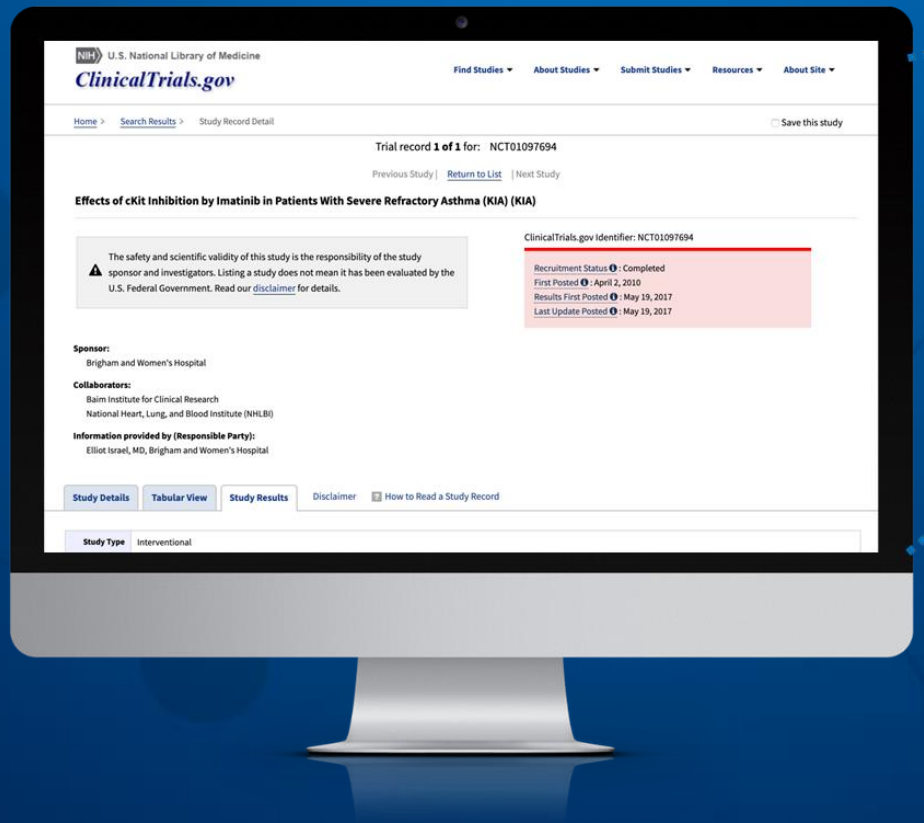
- Does NOT prescribe how study should be conducted
- Summary results at the end of the trial
  - No interim or “real time” reporting; no participant level reporting
- Information currently targeted at readers of the medical literature
  - “Tables” of information/“just the facts”; no conclusions or discussion
- 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

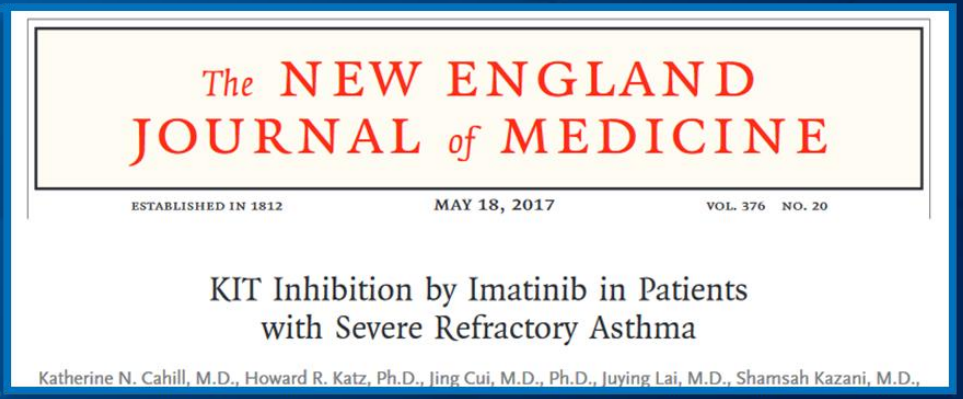
Registration, Results Submission and Publication

- 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

*Laine C et al. Ann Intern Med. 2007; http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Complementary to Publications





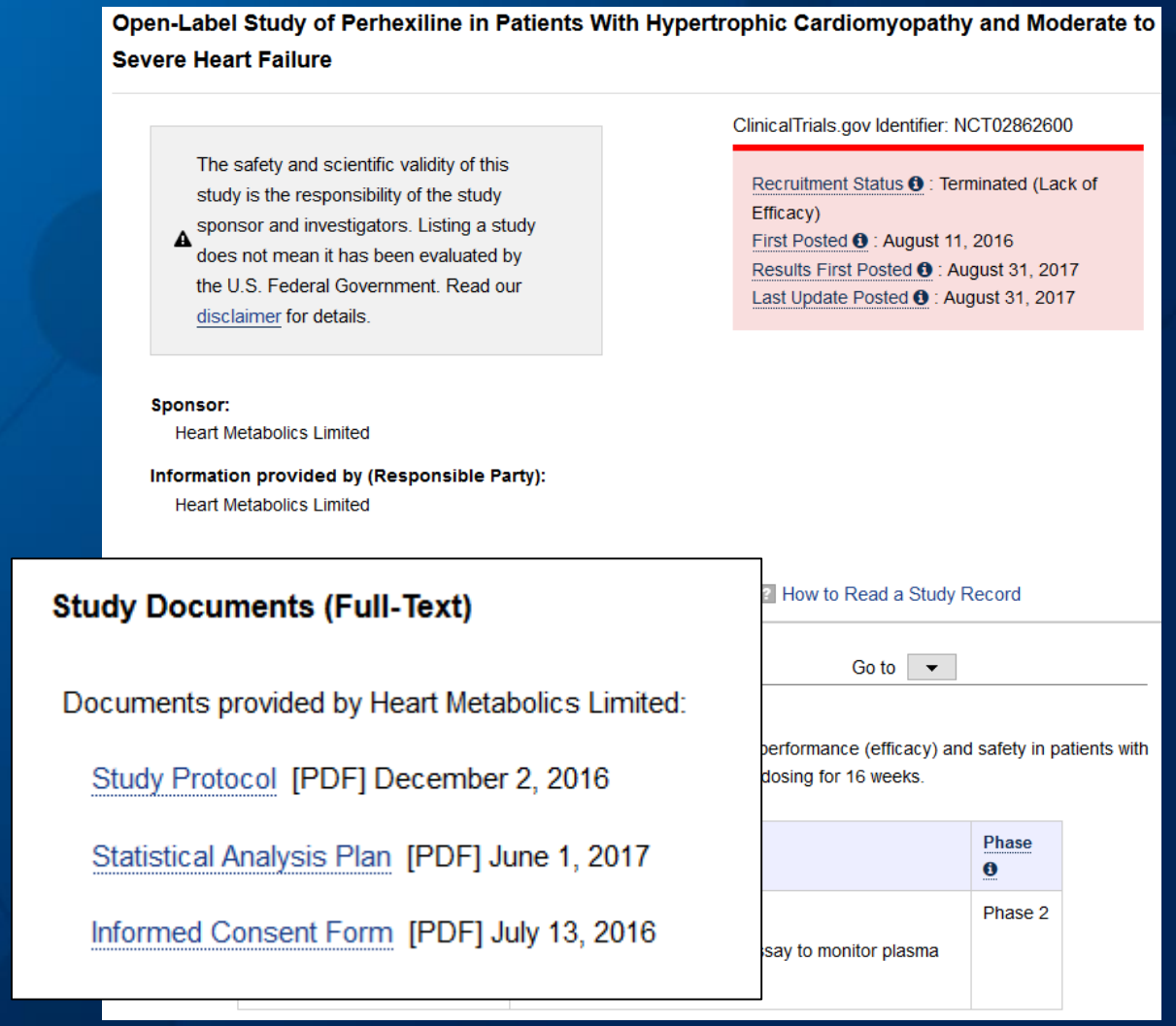
"A total of 27 secondary outcome measures were prespecified in the protocol; we report data for 21 of these outcomes in this article and in the Supplementary Appendix. The data and status for all primary and secondary outcomes are available at ClinicalTrials.gov (*https://clinicaltrials.gov/ct2/show/results/NCT01097694*)."

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

https://www.regulations.gov/docket?D=HHS-OPHS-2018-0021

Current: Results information submission

Update study record

Submit study record

Backend Processing

Responsible Party

QC Review Staff

1 **Sponsor Account**

2 Registration Information

Results Information

Automated Validation

3 Manual Validation Quality Control Review

No "Major" Issues

"Major" Issues

ClinicalTrials.gov

4 **Public Posting**

Address QC Review Issues

QC Review Comments

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

Update study record

Submit study record

Backend Processing

Responsible Party

QC Review Staff

1 **Sponsor Account**

2 Registration Information

Results Information

Automated Validation

3 Manual Validation Quality Control Review

No "Major" Issues

"Major" Issues

ClinicalTrials.gov

4 **Public Posting**

General Notice and Standard QC Review Comments

Address QC Review Issues

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

http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

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

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

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

http://grants.nih.gov/grants/guide/notice-files/NOT-CA-15-011.html

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

- Zarin DA, Tse T, Williams RJ, Rajakannan T. Update on trial registration 11 years after the ICMJE Policy was established. *N Engl J Med*. 2017 Jan 26;376(4):383-391.
- Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov - the final rule. *N Engl J Med*; 2016 Nov 17;375(20):1998-2004.
- Zarin DA, Tse T, Ross JS. Trial-results reporting and academic medical centers. *N Engl J Med*. 2015 Jun 11;372(24):2371-2.

Zarin DA, Fain KM, Dobbins HD, et al. 10-year update on study result submitted to ClinicalTrials.gov. N Engl J Med 2019; 381:1966-1974. DOI: 10.1056/NEJMsr1907644

Hudson KL, Lauer MS, Collins FS. Toward a new era of trust and transparency in clinical trials. *JAMA*; 2016 Oct 4;316(13):1353-1354.

Thank you

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Questions? register@clinicaltrials.gov