ClinicalTrials.gov Registration and Results (CTRR) Taskforce

Best Practice and General Procedure

High Level Overview of ClinicalTrials.gov Reporting where the Institution is the Responsible Party

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Best Practice

Institutional PRS Administrators can ensure study compliance with ClinicalTrials.gov requirements if:

- the Institution has a Compliance Audit to QA trials for ClinicalTrials.gov registration requirement
- the PRS Administrator has access to Institutional Review Board (IRB) applications
- the Research Team uses a Clinical Trials Management System (CTMS), maintained according to institutional policy, to which the PRS Administrator has access
- the Research Team is aware of ClinicalTrials.gov requirements via Institutional outreach, education, and effective email communications
- the Research Team is responsive to email queries relevant to ClinicalTrials.gov records
- the Institution has an escalation plan/policy for unresponsive Research Teams

Purpose / Background

ClinicalTrials.gov is a publicly available registry of clinical trials launched in February 2000 in response to the Food and Drug Administration Modernization Act (FDAMA) of 1997 and subsequently modified to include a results database in response to the Food and Drug Administration Amendments Act (FDAAA) of 2007. It is a service of the National Institutes of Health (NIH), developed by the National Library of Medicine, with the objectives of enhancing participant enrollment, providing a mechanism for tracking subsequent progress of clinical trials, ensuring scientific integrity, providing a resource for clinical trial participants, and transparent reporting clinical trials results to the benefit of public health. The database is widely used by participants, physicians, and medical researchers involved in clinical research studies.

Registration (and record maintenance) is required when:

- The trial is an "Applicable Clinical Trials" (ACTs) per FDAAA Law, required to be registered to ClinicalTrials.gov within 21 days of the first participant's enrollment.
    - The FDAAA Decision Tree helps determine whether a study is an ACT
- An investigator is NIH-funded for a clinical trial as of January 18, 2017, required to be registered within 21 days of the first participant's enrollment.
- The study is Interventional (Intervention per protocol as for a clinical trial, as opposed to Observational where the intervention is not assigned per protocol) per the International Committee of Medical Journal Editors' (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which requires registration prior to the first participant enrollment as a contingency for subsequent publication.
- The study evaluates a therapeutic item or service that falls within Medicare benefit category per the Centers for Medicare and Medicaid Services (CMS)

Results Reporting is required by FDAAA Law for ACTs and by the NIH for NIH-funded clinical trials. ICMJE encourages results reporting but does not currently *require* it.

Non-compliance in registration, maintenance, and results reporting has potential legal, civil, monetary, reputational, publication, and funding relevant consequences. Per FDAAA Law, non-compliance can cost the Responsible Party up to $14262/study/day of non-compliance (2023). Failure to comply with registration and results reporting requirements per NIH can result in revocation of current and future funding. Failure to register and make publicly transparent protocol updates can result in refusal to publish results per ICMJE guidance.

Institutions and Organizations who support clinical trials require systems to facilitate compliance and reduce organizational risk. This document proposes a high-level process for ClinicalTrials.gov Reporting.

This document applies to PRS Administrators who can review, update, edit, and release their Institutional ClinicalTrials.gov records.

Given the above regulations, centralized ClinicalTrials.gov reporting services staffed by PRS Administrators provide a valuable service to Research Teams and their Institutions.

It is the responsibility of Research Teams to initially determine if their study meets the registration and results reporting requirements. The IRB application documents the trial's ClinicalTrials.gov registration requirement and results reporting requirements are determined through the accurate population of the Oversight and Study Design sections of the ClinicalTrials.gov registration record (which identifies whether the study is an ACT) and the disclosure of relevant NIH-funding in the Secondary ID section (which identifies results due per NIH Policy).

The Institution audits IRB-approved studies to both to monitor ClinicalTrials.gov registration and to follow up with Research Teams to recommend registration if deemed applicable.

A general process for study registration, maintenance, and results reporting follows.

Procedures

Study Registration to ClinicalTrials.gov

The PRS Administrator registers relevant Investigator Initiated Trials (IITs; industry-sponsored trials are generally the responsibility of the Industry Sponsor, unless the Investigator holds the IND/IDE) to ClinicalTrials.gov on behalf of the Research Team using the following general process [see ClinicalTrials.gov Registration Best Practice for details]:

- **Notification:** PRS Administrator runs a weekly report out of the IRB application (or is otherwise notified of relevant IRB submissions) to identify studies submitted to the IRB pending initial approval in the past week for which the Research Team is responsible for ClinicalTrials.gov registration.
- **Communication**: PRS Administrator reaches out to the Research Team to offer assistance in registering their study to ClinicalTrials.gov. Upon reply:
    - **PRS Administrator populates** the ClinicalTrials.gov record with information from the Protocol and relevant IRB documents.
        - The PRS Administrator provides the Research Team with access to ClinicalTrials.gov (user accounts for PI and POC as identified by Research Team) and requests that they review the record
        - The Research Team approves or submits changes
        - The PRS Administrator releases the record for PRS Review
        - The ClinicalTrials.gov PRS completes their review in 2-5 business days and
            - assigns an NCT number, or
            - responds with comments to address
                - The PRS Administrator recommends changes and receives approval from the Research Team prior to re-releasing the record.
    - OR, if the **Research Team populates** the initial Registration Record, the PRS Administrator is notified that a record is ready for review.
        - PRS Administrator reviews the registration record according to the PRS Review Criteria
        - The PRS Administrator recommends edits to the registration record with Research Team permission.
- After **assignment of NCT number**, the PRS Administrator emails the Research Team's POC to:
    - Notify Research Team that NCT number is assigned, where to enter it into the CTMS, and indicates maintenance requirements (consider email script).

- If the trial is an Applicable Clinical Trial (ACT) per FDAAA, share results reporting requirements with the Research Team.

Maintenance: Study Status Changes

The PRS Administrator changes the study status in the ClinicalTrials.gov record, using the following process [See ClinicalTrials.gov Maintenance Best Practice for details]:

- If the Research Team maintains a CTMS
  - The PRS Administrators can receive a 'status change' notification. Confirm that the study has a ClinicalTrials.gov registration record and reach out to the Research Team to offer to make the status change.
  - The PRS Administrators can run a weekly report to identify study status changes. Confirm that the study has a ClinicalTrials.gov registration record and reach out to the Research Team to offer to make the status change.
- If the Research Team does not use CTMS to curate trial data, then either:
  - The Research Team proactively updates their ClinicalTrials.gov record within 30 days of status change
  - The Research Team reaches out to the PRS Administrator within 30 days of status change to update the status of their trial on ClinicalTrials.gov, or
  - The PRS Administrator confirms the status when Protocol Amendments (see below) are approved, or
  - The PRS Administrator confirms the status via the Annual Record Verification process

Maintenance: Protocol Amendments

The PRS Administrator makes changes to the ClinicalTrials.gov record to reflect applicable institutional study changes including protocol amendments, change of Principal Investigator, participating site additions or withdrawal, relevant study team changes (particularly for record access), and funding/collaborator changes as required [See ClinicalTrials.gov Maintenance Best Practice for details].

- **[IRB application]:** PRS Administrator runs a weekly report out of the IRB application. The report can identify:
    - **Initial IRB Approvals** – See Registration Above
    - **IRB Approved Change Reviews -** The PRS Administrator reviews the change of protocol to identify whether the approved amendment requires edits to the ClinicalTrials.gov registration record.
        - The PRS Administrator reviews the current version of the protocol to assist in amending the ClinicalTrials.gov record. Offer assistance in making relevant changes to the ClinicalTrials.gov record [email script], with reply, PRS Administrator either:
            - Makes minor edits (ie. small change to eligibility criteria or anticipated enrollment), the PRS Administrator approves and releases the record to keep the record current.
            - PRS Administrator emails the Research Team, indicating changes made per amendment
        - Seeks approval for changes made to the study record from the Research Team prior to releasing the record (for major changes to the study model or intervention)
        - Requests that the Research Team verify that the registration record is up to date
    - **IRB Approved Continuing Reviews** – Continuing Reviews indicate the study status at a particular point in time and can be useful to QA the study status in records that are not documented in CTMS

Maintenance: Annual Verifications

ClinicalTrials.gov requires that records are reviewed and verified annually [See ClinicalTrials.gov Maintenance Best Practice for details]. The PRS Administrator uses the Planning Report to identify studies that are due for annual verification and emails the Research Team to request they confirm the Public ClinicalTrials.gov record is up to date with respect to the most recently approved protocol.

Results Reporting in ClinicalTrials.gov

- Submission of summary results for “Applicable Clinical Trials” (or relevant trials per NIH Policy) is due no later than 12 months after the study’s Primary Completion Date (defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. This often corresponds with the final participant’s Off Treatment or Off Study date). [See Results Reporting Best Practice for details]
- ClinicalTrials.gov provides detailed instructions on results reporting, as well as results templates
    - Tutorials: https://prsinfo.clinicaltrials.gov/tutorial/content/index.html#/
    - Instructions: https://clinicaltrials.gov/ct2/manage-recs/how-report
    - Templates: https://prsinfo.clinicaltrials.gov/results_table_layout/ResultSimpleForms.html
- The PRS Administrator uses the **Planning Report** [see ClinicalTrials.gov Maintenance Best Practice] to identify studies for which results are due. They contact the study team ~1 year to 6 months in advance of when results are due to facilitate the process, following applicable escalation process for non-responsive Research Teams.

Applicable Regulations and Guidelines

- ClinicalTrials.gov overview: https://clinicaltrials.gov/ct2/manage-recs
- Compliance for NIH awardees: https://grants.nih.gov/policy/clinical-trials/reporting/steps.htm
- Elaboration of definitions of “Responsible Party” and “Applicable Clinical Trial”: http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf
- Institutional support for clinical trials registration and results reporting [link]

- International Committee of Medical Journal Editors' (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals: http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/

Glossary

ACT: Applicable Clinical Trial

CMS: Centers for Medicare and Medicaid Services

ClinicalTrials.gov: ClinicalTrials.gov (https://register.clinicaltrials.gov/)

FDA: Food and Drug Administration, federal agency of the US Department of Health and Human Services.

FDAAA: Food and Drug Administration Amendments Act

FDAMA: Food and Drug Administration Modernization Act

ICMJE: International Committee of Medical Journal Editors (http://www.icmje.org/)

IIT: Investigator-Initiated Trial

IRB: Institutional Review Board

NCT: National Clinical Trial, the NCT number is assigned by ClinicalTrials.gov upon acceptance of the registration record

NIH: National Institute of Health

PI: Principal Investigator

POC: Point of Contact

PRS: Protocol Registration and Results System

Research Team: This is the study team that includes the PI, study coordinators, and program managers per the IRB application

Document History

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