Institutional ClinicalTrials.gov Best Practice

Meredith Rhodes, University of Wisconsin-Madison
Sarah Snider, Medical University of South Carolina
Carlee Brueser, Duke University
Susan Hmwe, City of Hope Comprehensive Cancer Center

Background

ClinicalTrials.gov was launched in 2000 in response to the Food and Drug Administration Modernization Act (FDAMA) of 1997 requiring the creation of a public database for drug interventions to connect potential participants with innovative and potentially life-saving treatments. Subsequent changes to the law via the Food and Drug Administration Amendments Act (FDAAA) of 2007 to its 'Final Rule' in 2017 provide a legal definition of Applicable Clinical Trials (**ACTs**) for which the law applies and details about registration, maintenance, and results reporting to remain in compliance with the law.

With a public registry for clinical trials in place to meet legal requirements, other entities have taken advantage of the ClinicalTrials.gov platform for their own purpose.

- [**2005**] The International Committee of Medical Journal Editors (**ICMJE**) created a policy encouraging scientific integrity and transparency by requiring clinical trials have a National Clinical Trials (NCT) number (be submitted to ClinicalTrials.gov) prior to first participant enrolled as a contingency of publication.
- [**2007**] Centers for Medicare & Medicaid Services (**CMS**) require qualifying clinical trials registered to the public database.
- [**2015**] CMS mandates National Clinical Trial (**NCT**) numbers are reported on all claims.
- [**2017**] The National Institutes of Health (**NIH**) Policy on the Dissemination of NIH-Funded Clinical Trial Information expanded upon FDAAA Law requiring clinical trials of any phase per NIH definition (including behavioral and basic science study) to maintain records and report results to ClinicalTrials.gov.

- [**2019**] The revised Common Rule (45 CFR 46.116(h)) requires that any clinical trial conducted or supported by a Common Rule department or agency, must post one informed consent form that was used on the study in enrolling participants on a publicly available Federal website within a specific time frame. ClinicalTrials.gov and Regulations.gov are the currently approved federal websites.
- [**2019**] ICMJE required the description of an Individual Participant Data (**IPD**) Sharing Plan at registration to ClinicalTrials.gov to encourage researchers to share and leverage data from participant volunteers.

The result of layering additional requirements with differing expectations on a framework not designed with their compliance in mind is confusion, frustration, and reactivity toward compliance. It also buries the bigger picture of why the database was established in the first place, *as a participant-centered resource*.

Historically, the cost of noncompliance in public clinical trials records has largely been ignored as threats of financial and legal action per FDAAA Law (enacted in 2007) had not been acted upon until 2021. Universities now recognize the need for ClinicalTrials.gov Services to assist researchers and study teams with various registration, maintenance, and results reporting requirements to ClinicalTrials.gov to mitigate institutional risk.

However, mitigating institutional risk is not the primary purpose of clinical trials.

Academic Institutions demonstrate leadership and Good Clinical Practice (GCP) in clinical trials efforts by offering **ClinicalTrials.gov Best Practices** to ensure participant volunteers and their families have access to public information and summary trial results for trials they consent to at their Institution. This **participant-centered** approach prioritizes the ethical obligation to clinical trials volunteers and demonstrates scientific integrity and transparency of the Institution's clinical research ecosystem. In alignment with values of patient-centeredness, professionalism, scholarship, stewardship, health equity, integrity, accountability, social responsibility, and diversity and inclusion, ClinicalTrials.gov Best Practice builds community trust, positions the ethical obligation to participants over minimal legal and policy requirements of outside entities, ensures compliance, and elevates the importance of the entire clinical trials enterprise within the Institution and beyond. The Institution has a ClinicalTrials.gov Service uniquely positioned to support this mission.

Why ClinicalTrials.gov? Public Clinical Trials Stakeholder Perspectives

Clinical trials transparency advocates identify 4 levels of clinical trials information important to the public:

- What clinical trials have been conducted?
- Brief summary of results with full study protocol with statistical analysis plan
- Full study report for marketing authorization or CONSORT statement
- Individual participant data

Protocol Registration and Results Reporting to ClinicalTrials.gov satisfy the first 2 bullets and provide insight into the accessibility of the last 2. This information is important for many stakeholders.

Participant Perspective

- Registration to the public provides information to potential participants & referring clinicians about potentially lifesaving treatments
- Transparency in clinical trial information fulfills an ethical obligation to participants in research that they volunteer to take part in
- Access to study protocols and statistical analysis plans helps all stakeholders understand the context of study results

General Public Perspective - The general public holds within it the pool of future participants

- Public clinical trials records promote scientific integrity and transparency
- Transparency and communication builds trust between researchers and under-represented communities
- Provides a mechanism to demonstrate the responsible allocation of government funds, which are ultimately derived from the citizenry.

Researcher Perspective

- Public clinical trials records enhance study recruitment
    - Dynamic records show when study sites are recruiting
    - Protocol records indicate participant populations of interest
    - ClinicalTrials.gov public site provides source data for clinical trials search engines
- Summary results reduce publication bias and provide new data of interest quickly

- Results Module provides several places to 'show your work' in service to the research community. Why was an outcome measure not measurable per protocol? What were barriers to study completion? What limitations and caveats are there to reported results? Who can researchers contact to learn more from your efforts?

Research Community - Ultimately in the interest of Policy Makers and the General Public

- Availability of summary results and de-identified individual participant data enables leverage of existing volunteer efforts, providing data for additional IRB-approved study
- Promote efficient allocation of research funds
- Clarity around the scope of clinical trials already conducted helps researchers avoid duplicative efforts
- Provide a public mechanism to identify and understand the evidence base for specific biomedical questions

Policy Makers

- Understanding the full list of clinical trials conducted and the data collected provides policy makers with data to make the most informed decisions
- Provides a central catalog of research addressing public health issues; ie COVID-19 pandemic

Institutional ClinicalTrials.gov Best Practice Summary

- **Institutional ClinicalTrials.gov Service** established to assist teams to keep ClinicalTrials.gov records in compliance
    - Streamlining research support services to work in parallel with one another can facilitate compliance with study registration requirements. For example, when a study is reviewed for billing compliance purposes, a review can also be done to identify if study needs to be registered to ClinicalTrials.gov
    - Conduct one-on-one consultations with study teams who are new to the registration process.

- **Clinical Trials** that meet the definition per ICMJE (below) **are registered to ClinicalTrials.gov** and assigned NCT number **prior to first participant enrollment** to comply with ICMJE publication contingency. ICMJE and the journals who follow ICMJE guidance have a more stringent registration requirements than federal entities.

- This is achievable if IRB applications indicate the study is a clinical trial per the definition and ClinicalTrials.gov Service has reporting capabilities to see what studies are within scope.
- This is achievable if the Institution utilizes a Clinical Trials Management System (CTMS) that has clear data field definitions and expectations to keep study activities updated in real time.
- As Observational Trials involve consenting human participants, they are within scope of the Declaration of Helsinki and are encouraged to be registered to ClinicalTrials.gov

- **NCT numbers listed on all consent forms** to connect participants to public records and results for the trials to which they volunteer
  - NCT numbers either assigned prior to full Initial IRB approval or submitted as an amendment.
  - Achievable if NCT number required in CTMS prior to Open to Accrual

- **Clinical Trials with ClinicalTrials.gov records are maintained in a CTMS.** The following components relevant to the dynamic ClinicalTrials.gov record are updated in real time:
  - *Protocol Registration and Maintenance*
    - Study Status
    - Accrual
    - IRB-approved Protocol Amendments (with tracked changes)
    - Anticipated/Actual Primary and Study Completion Dates
    - Study Contacts
  - *Results Module*
    - Participant Demographics
    - Adverse Events (as relevant)

- **Individual Participant Data (IPD) Sharing Plan exists** at the time of registration and IPD is accessible and timely for relevant, appropriate, and IRB-approved studies as outlined in the plan
  - To contribute to the scientific community and leverage participant efforts
  - Achievable if there is an Institutional Policy and/or resources to secure digital data

- **Prompt communication** with ClinicalTrials.gov Service regarding public ClinicalTrials.gov records will ensure compliance is maintained as all relevant clinical trial changes are updated to the public record within 30 days of the change.

- **All Institutional Clinical Trials submit Summary Results** within 1 year of the date that data collection is completed for the Primary Outcomes (Primary Completion Date)
    - In ethical obligation to participants
    - To reduce publication bias
    - To manage expectations
    - In service to the research community

- **Informed Consent Form (ICF) to be uploaded** within 60 days of the last participant's last visit (Study Completion date per ClinicalTrials.gov) in the interest of transparency and per the Revised Common Rule

Definitions

Applicable Clinical Trial (ACT): [Per FDAAA Law] A controlled, prospective interventional trial using an FDA-Regulated drug (other than Phase 1), device (other than small feasibility), or biologic intervention for the purpose of studying health outcomes, conducted in the US.

- For device trials, an ACT is defined as, "a prospective clinical study of health outcomes comparing an intervention with a device product subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device product, or a clinical trial to test prototype device products where the primary outcome measure relates to feasibility and not to health outcomes)."
- For drug trials (including biological products), an ACT is defined as "a controlled clinical investigation, other than a Phase 1 clinical investigation, of a drug product subject to section 505 of the Federal Food, Drug, and Cosmetic Act or a biological product subject to section 351 of the Public Health Service Act, where "clinical investigation" has the meaning given in 21 CFR 312.3 (or any successor regulation) and 'Phase 1' has the meaning given in 21 CFR 312.21 (or any successor regulation)."

ClinicalTrials.gov: The public database for Protocol Registration and Summary Results Reporting. [https://clinicaltrials.gov/]

Clinical Trial: As defined by the International Committee of Medical Journal Editors (ICMJE), any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.

Clinical Trial Management System (CTMS): Software / integrated database used to document and manage all aspects of clinical trials conduct from budgeting, calendaring, multi-site coordination, study staff, study status, participant accrual, protocol and informed consent versions, scientific reviews, FDA regulatory actions, IRB approvals, data safety monitoring, protocol deviations, adverse events, participant demographics with integrations to electronic medical records, clinical trials search engines, IRB processes, reporting and analytics products. Well-defined CTMS process provides a single source of truth for clinical trials.

Good Cause Extension: A responsible party may request an extension of the results submission deadline for Applicable Clinical Trials and NIH-funded clinical trials. The request must be submitted in the PRS prior to the date results are due. This must be at least one day before the results are scheduled for submission. The request must include reasons that demonstrate good cause for an extension, as well as an estimated date of submission. In general, there are very limited situations that are considered ‘good cause’. The Director of the NIH will review the request and notify the responsible party whether an extension has been granted.

Good Clinical Practice (GCP): A set of internationally recognized standards for designing, conducting, performance monitoring, auditing, recording, analysis, and reporting of clinical research that involve human subjects. Compliance with this standard helps to provide public assurance that the rights, safety, and welfare of human subjects in research are protected; that the research is consistent with the principles that have their origin in the Declaration of Helsinki; and that the data collected are reliable and credible. Three basic principles of GCP are respect for persons, beneficence, and justice.

Individual Participant Data (IPD) Sharing Plan: Indication of an IPD Sharing Plan is required for all trials registered to ClinicalTrials.gov per ICMJE guidance. An IPD Sharing Plan addresses whether IPD will be available to other researchers, what data will be shared, what documents will be available, the timeframe of data availability, who is within the plan's scope, what types of analyses are permissible, and how will the data be shared. In the spirit of transparency and scientific reproducibility, the IPD Sharing Plan must be outlined in trial-related publications per ICMJE Guidance.

National Clinical Trial (NCT) Number: An NCT number is an 8-digit identifier that begins with the letters 'NCT' (11 characters total). An NCT number is assigned by ClinicalTrials.gov Protocol Registration and Results System (PRS) reviewers after an initial registration record is submitted and returned with no major comments as approved to be posted to the public site.

Protocol Review and Results System (PRS): The website and user interface where PIs and their delegates populate and edit ClinicalTrials.gov Registration Records and Summary Results to submit to PRS Reviewers for approval and update of the public record posted on ClinicalTrials.gov. [https://register.clinicaltrials.gov/]

PRS Administrators: Position with access to Institution ClinicalTrials.gov Records. Can serve a variety of functions depending on Institutional policies.

- **Responsible Party is PI:** PRS Admin consult with study teams and facilitate records compliance
- **Responsible Party is Institution:** PRS Admin review all ClinicalTrials.gov records to release for PRS Review

Qualifying Trial: A clinical trial that is qualified for coverage, as specified in the Medicare National Coverage Determination (NCD) Manual, Section 310.1. If a trial does not "qualify" under the Clinical Trial Policy, then the costs for all items and services related to the clinical trial cannot be billed to Medicare. The National Clinical Trial (NCT) number that is assigned after registering a trial on ClinicalTrials.gov must be included on all insurance claims for qualifying trials.

World Medical Association (WMA) Declaration of Helsinki: An evolving set of ethical principles for medical research involving human subjects, last updated in 2013 to include declarations on Research Registration and Publication and Dissemination of Results:

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

References

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- https://register.clinicaltrials.gov/ - PRS website
- https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf - ACT determination
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- http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html - ICMJE
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- https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies - CMS Clinical Trial Policies
- https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ - Declaration of Helsinki

Document History

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