ClinicalTrials.gov Registration and Results (CTRR) Taskforce

Best Practices and General Procedure

ClinicalTrials.gov Registration Where the Institution is the Responsible Party and the PRS Administrator Populates a Draft Record

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Best Practices for PRS Admins to Register a study to ClinicalTrials.gov

- **Identify Clinical Trials that will be Registered**: Have a system in place (ie. ClinicalTrials.gov Protocol Registration and Results System (PRS) Administrator access to Clinical Trials Management System (CTMS) reporting or ability to report from Institutional Review Board (IRB) application) to learn when studies requiring ClinicalTrials.gov records have either been submitted for Initial IRB review or have received Initial IRB approval.

- **Initiate Communication**: Proactively offer your services to the team.

- **Access the Protocol:** Ensure access to the study protocol in the IRB application, CTMS, or wherever the final IRB-approved document is required to be maintained. Access to the protocol in this location facilitates subsequent public record maintenance requirements.

- **Utilize** the PRS Review Criteria to facilitate assignment of National Clinical Trial (NCT) number on initial submission.

- **Customize the Secondary ID field** in the Study Identification section for internal purposes. For example, tracking the Protocol Version Date represented in the record or the Principal Investigator's Department can assist in compliance, Institutional public records metrics, and identifying groups responsible for trial results data.

- **Know Your Audience:** The ClinicalTrials.gov record will be sourced for custom purposes and the Brief Summary and Eligibility Criteria are likely to automatically populate local clinical trials search engines. Keep these fields succinct and informative for participant recruitment.

- **Confirm Results Reporting Requirement** with Study Team at the time of registration. Require study team to confirm whether their trial is an Applicable Clinical Trial (ACT) and is therefore registered as such, or is within the scope of NIH Data Dissemination Policy and relevant grant information is populated accordingly.

- **Educate the Study Team**: When the draft registration is populated, use this opportunity to give the study team a tutorial on how to access and review their record. Create PRS User Accounts as required and arrange a virtual meeting to have them share their screen as they log into the PRS and navigate their record.

- **Create a Template "Next Steps" Email** to notify the study team of the assignment of the NCT number and to prepare them for required record maintenance, Informed Consent Form (ICF) posting and results reporting requirements, as relevant.

- **Create a Customer Feedback Survey** to learn how to improve your service.

Purpose

The [PRS Administrator] registers trials to ClinicalTrials.gov on behalf of the Principal Investigator (PI) and Study Team. This document recommends a ClinicalTrials.gov registration procedure for the [PRS Administrator's].

[Institutional] ClinicalTrials.gov Policy

All [Institutional] faculty, staff, and students conducting human subject research under University oversight are expected to follow [insert federal registration and results reporting requirements regarding ClinicalTrials.gov or link to institutional policy here].

Background

ClinicalTrials.gov is a publicly available registry of clinical trials data. 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 of clinical trials results to the benefit of public health. The database is widely used by participants, physicians, and medical researchers, in particular those involved in clinical research studies.

Registration is required when any of the following conditions are met:

- The Food and Drug Administration (FDA) requires registration for all Applicable Clinical Trials (ACTs) on ClinicalTrials.gov within 21 days of the first participant's enrollment.
    - ACTs are clinical trials of FDA-regulated drug, biologic, or device products
    - Use the ACT Checklist for help in determining whether a study is an ACT
- NIH-funded clinical trials – Studies that are directly funded in whole or in part by the NIH
- The International Committee of Medical Journal Editors' (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals require ClinicalTrials.gov registration **prior to enrollment of the first participant as a condition of consideration for publication.**
- Centers for Medicare and Medicaid Services (CMS) requires registration for qualifying trials that evaluate a therapeutic item or service that falls within the Medicare benefit category.

Determine Results Reporting Requirement at Registration

At the time of registration, it is important to look ahead toward results reporting requirements, to ensure the registration record is accurately populated to avoid later problems. In particular, all primary and secondary outcome measures that are prespecified in the protocol must be registered. If the protocol is amended during the study, the registration must be updated to reflect the changes in the amendment, including changes to outcome measures.

Results will be required if the trial is 1) an ACT per FDAAA Law or 2) an NIH-funded Clinical Trial (initially funded after 1/18/2017)

Applicable Clinical Trial per FDAAA Law - Per FDA regulations, the sponsor must **submit results** to ClinicalTrials.gov if the study is an "Applicable Clinical Trial" as defined in US Public law 110-85, Title VIII, Section 801.

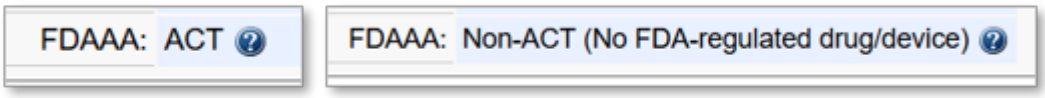
- Applicable clinical drug trials include: Controlled clinical investigations, other than Phase 1, of drug or biologic products subject to US FDA regulation
- Applicable clinical device trials are: Controlled trials with health outcomes of devices subject to FDA regulation (other than small feasibility studies) and pediatric post market surveillance studies of device products that are ordered by the FDA

Here is a Checklist for Evaluating Whether a Clinical Trial or Study is an ACT

For assistance determining whether a trial studies an FDA approved drug or device, try this query tool (created by Jake Rome at University of Wisconsin - Madison)

The determination of whether a trial is an ACT is documented at Initial Registration.

Source data in the ClinicalTrials.gov Registration Record automatically populates an 'ACT' determination on the Record Summary Page.



The following data elements are used by the Protocol Registration and Results Reporting System (PRS) to determine whether the registration is of an ACT (these data elements are tagged throughout this document as 'ACT Determination'):

- Study Type
- U.S. FDA-Regulated Drug and/or Device
- Intervention Type
- Study Phase
- Primary Purpose
- Facility Location
- U.S. FDA IND/IDE Study
- Product Exported from U.S.
- Study Start Date
- Primary Completion Date
- Study Completion Date
- Overall Recruitment Status

NIH-funded Clinical Trial - A clinical trial directly funded in whole or in part by NIH, regardless of study phase or intervention type (NIH Policy on Dissemination of NIH-Funded Clinical Trial Information) will be required to report results within 1 year of Primary Completion

- If within the scope of NIH Policy, it is important to include the grant number in the Secondary ID field of the registration record, as outlined below
- The grant number will prompt the appropriate NIH organization to be listed as a Collaborator on the record, as outlined below
- Documentation of NIH funding at registration will facilitate results reporting compliance as required by NIH Policy

Procedure

This document provides a procedure for the [PRS Administrator] to register a trial to ClinicalTrials.gov for any of the above reasons. This process assumes the clinical trial requires a registration record per the Study Team and the [PRS Administrator] is aware of this.

1. **Communicate:** If the [Institutional] Principal Investigator is responsible for the registration, the [PRS Administrator] contacts the Study Team to either:

a. Let them know you will be registering the study to ClinicalTrials.gov on behalf of the PI and Study Team [generate an email script], or
b. Introduce yourself and offer registration service. Inform the team that in total the typical total registration takes approximately of 2-3 weeks, including time for ClinicalTrials.gov QC review [generate an email script]
    i. The [PRS Administrator] finds out if the trial will be curated in [CTMS]. If yes, then review the trial's [CTMS record] for required information.
    ii. If the Study Team will not use a [CTMS], confirm a communication plan to ensure record maintenance actions can take place.

2. **Educate:** If the resources are present, this is an opportune time to offer a virtual (or face to face) consultation for study team members who are new to the PRS. If a consultation is requested, confirm date and time via calendar invite and explain that during the consultation, the study team member will share their screen while the PRS administrator walks them through each step of the registration process.
3. **Organize**: For Institutional Investigator Initiated Trials (IITs) that will be registered:
    a. Create a new folder for the study on [server name]. Suggested: name according to [PI Name], with subfolders by IRB Number or trial keyword. Use this folder to save
        i. Previews sent for review
        ii. Drafts
        iii. Results-related documents
        iv. Copy of all important communications – at a minimum, all approvals (e.g., Initial approval by PI to release record to PRS for review)
    b. Add a study folder in the service [email] inbox, organized by PI and study IRB number / NCT number
    c. A different system might be utilized to maintain related files and document approvals (e.g., REDCap, Smartsheet)
4. **Register**: To register a trial on ClinicalTrials.gov (Fields that are part of the **ACT determination** are noted as such):
    a. Log into PRS (https://register.clinicaltrials.gov)
    b. Click link for "New Record," located in the Records menu

c. Complete the ClinicalTrials.gov data fields per the ClinicalTrials.gov Protocol Data Element Definitions (available on each page in the "Definitions" link, which will open a new window. The "Help" link provides further examples and explanations). Utilize the ClinicalTrials.gov Protocol Registration Quality Control Review Criteria for guidance.

i. **Organizations Unique Protocol ID**: e.g., IRB number or [CTMS] record number

ii. **Brief Title**: Should be in lay language; remove technical study design terms (ie, Phase 1; Randomized etc.)

- The Brief Title appears as the link to the study record on the ClinicalTrials.gov public site, so it should be short and understandable
- Acronym: Leave blank unless there is an acronym associated with the study

iii. **Study Type**: (**ACT Determination**: interventional, observational, expanded access protocol)

- Note: single patient expanded access protocols do not require ClinicalTrials.gov registration
- Click 'Continue'

iv. **Official Title:** Protocol title, this can include study design terms

v. **Secondary IDs**: *include*

- NIH Grant/Contract Award Number as identified in the IRB application
- Registry ID: CTRP's NCI Trial ID number for cancer relevant studies
- Other: IRB number
- Other: department within which trial is run
- Other: Protocol Version date (update this date with subsequent protocol amendments)
- Click 'Continue'

vi. **Record Verification Date:** Use Current Month / Year

- Setting this date means that the entire record has been reviewed for accuracy and completeness

vii. **Overall Recruitment Status:** *generally* 'Not Yet Recruiting', but consult Study Team for status if registering in retrospect (ACT determination)

- Note: 'Recruiting' means that potential participants will see contact information in the public record and can call to try to enroll; 'Enrolling by Invitation' means that contact information will be hidden in the public record (only invited participants can enroll)

viii. **Study Start Date** (**ACT Determination**)

- For Anticipated Dates, in general enter a date at least 1 month out from time of registration, and **populate the month and year only**. Populate the 'day' only if entering the Actual Study Start Date (this will assist with Maintenance efforts related to the Planning Report)
- Actual Study Start Date is the date the study actually opens to enrollment; if a participant is not enrolled on the day enrollment opens, the date will change to the date the first participant is enrolled (usually the date the first participant is consented). Use Anticipated Dates unless the study has already started.

ix. **Primary Completion Date** (**ACT Determination**)

- **Anticipated** Primary Completion Date is the projected last date that primary outcome measure will be obtained from an enrolled participant, this is a moving target.
- **Actual** Primary Completion Date is entered when that date has been reached, this will prompt you to include an Actual Enrollment number. It is uncommon that this date will be 'actual' at the time of initial registration.

x. **Study Completion Date** (**ACT Determination**)

- This is the last date that **any data** will be collected from an enrolled participant in the study. It will be the same as the Primary Completion Date if primary outcome measure data are collected for the entire duration of the study. If other data will still be obtained from enrolled participants after all primary outcome measure data have been obtained (e.g., for secondary or exploratory outcome measures or safety data), then the Study Completion Date will be later than the Primary Completion Date. Also a moving target.
- Click 'Continue'

xi. **Sponsor/Collaborators**

- Responsible party: **Sponsor** (default)
- Sponsor: [Institution] (default)
- Collaborators: per IRB application (institutions, not individuals are listed)
- Be sure to add NIH, NCI, or other federal collaborators as indicated by the registration records warnings (usually prompted by entry of a grant number in the Study Identification > Secondary IDs section).
- Click 'Continue'

xii. **Oversight:** The ACT Checklist can assist PIs with this info

- Is an FDA-regulated Drug being studied?: Yes or No (**ACT determination**)
- Is an FDA-regulated Device being studied?: Yes or No (**ACT determination**)
    - If Yes, then is it an Unapproved or Uncleared Device? If Yes, should it be posted prior to approval? Select Yes to protect the ability to publish results in an ICMJE journal (ICMJE requires public registration)
    - Is the study a Pediatric Postmarket Surveillance study of a device product ordered by the FDA?
- FDA IND/IDE: Yes or No (**ACT determination**)

- If the clinical investigation of the drug is “IND exempt”: Yes
- If Yes: You will need to note the FDA Center (CDER [drugs], CBER [biologics], CDRH [devices] – see Definitions link for ClinicalTrials.gov Guidance)
- Enter the IND or IDE Number per the protocol or [CTMS]
- IND or IDE not required if it is standard of care drug or no drug as an intervention

- Human Subjects Protection Review:
  - Board Status (Note: for interventional studies that are exempt from IRB review or for which IRB submission is not required, a copy of the notice of IRB determination must be provided to ClinicalTrials.gov before the status can be set to ‘Recruiting’ or ‘Enrolling by Invitation’; email to register@clinicaltrials.gov)
  - Approval Number: e.g., IRB Number
  - Board Name: [Name of body approving protocol]
  - Board Affiliation: [institution]
  - Board Phone
  - Board Email
  - Board Address
- Data Monitoring Committee: Yes or No – not required
- FDA Regulated Intervention - leave unselected; no longer required as a source field for ACT
- Section 801 Clinical Trial: leave unselected; no longer required as a source field for ACT
- Click ‘Continue’

xiii. For the Brief Summary, Detailed Description, Conditions, Study Design, Arms and Interventions, Outcome Measures, and Eligibility sections, use a combination of the Protocol, [CTMS], Informed Consent Form (ICF), and the IRB application as sources for information. Ask the Point of Contact (POC) if you have any questions the protocol does not answer.

- **Brief Summary** – Include a very brief **lay** description including the hypothesis, who are they recruiting (generally, i.e., participants with breast cancer), and how long the participant can expect to be on study. Note: this section is often sourced in online clinical trials recruiting applications, brevity, accessibility, and clarity are therefore important
- **Detailed Description** – not required, but can be used to provide background information and to copy relevant background information and specific aims from the protocol, note: references within the text are not allowed

Note: do not include outcome measures in the Brief Summary or Detailed Description, since ClinicalTrials.gov reviewers will check for consistency with the Outcome Measures Module

- **Conditions of Focus of Study** – add conditions and keywords as appropriate, this is for ClinicalTrials.gov search engine
- **Primary Purpose** – from [CTMS] or protocol (**ACT determination**)
- **Study Phase** – if an FDA-Regulated Drug intervention is being studied then a phase number is required (**ACT determination**), *general* description below:
    - N/A – non-drug trials
    - Early Phase 1 – e.g., exploratory study
    - Phase 1 – e.g., pharmacological/metabolism, dose levels
    - Phase 2 – e.g., safety and effectiveness, AE data
    - Phase 3 – e.g., larger group after Phase 2 to evaluate benefit
    - Phase 4 – e.g., study of already FDA-approved drugs (studies of approved drugs can be other than phase 4).
- **Interventional Study Model** – depends on how many arms
    - Single Group for 1 arm
    - Parallel for 2+ arms where each arm gets its own intervention for the duration of the study

    - Crossover for 2+ arms receive one intervention in an initial study period, and then switch to another in a subsequent period
    - Factorial for 2+ interventions, each alone and in combination, against a control group
    - Sequential for groups that change interventions at milestones, as in dose escalation studies
- **Masking**: What groups are unaware of the intervention the participant is assigned to? Study may be open-label.
- **Allocation**: Is this a randomized trial or non-randomized? Select “N/A" for single-arm studies.
- **Enrollment**: Target accrual at the beginning of the trial, this will become the ‘Actual’ number enrolled at ‘Closed to Accrual’
- **Arms (or Groups) and Interventions**: You’ll need to understand the study design and various intervention types to populate this section. If there are more than one arm and intervention, you will have to use the Cross-Reference to assign interventions to the appropriate arm or group
- **Outcome Measures:** often called “Endpoints” in the protocol, they are not the same things as ‘Objectives’ or ‘Aims’. All Primary and Secondary Outcome Measures must be included in the registration. Exploratory or Other Outcome Measures may be included but are not required. Multiple measurements cannot be included in a single outcome measure, e.g., “Number of Adverse Events and Discontinuations” would not pass ClinicalTrials.gov QC review, two outcome measures would be needed, one for adverse events, and one for discontinuations.
    - **Title:** be sure the title accurately describes the parameter to be measured, and add ‘Change in’ if it measures a change between time points

- **Outcome Measure Description:** if the measure includes a scale, define the scale, including total range of possible answers and what higher scores mean. If the scale includes sub-scales, include the name, full sub-scale range, what higher scores mean, and explain how the total score is calculated. If a description of the scale score is not included in the registration, ClinicalTrials.gov will make an “Advisory" QC comment but will still post the information on the public site. Scale score information *must* be included when submitting *results*.
- **Time Frame:** this is from the participant’s perspective, at what time point in the study will this measurement be made? For change measures, include the time points between which the change will be measured (e.g., baseline and week 1). Primary Outcome Measures collected at multiple time points that are not measuring a change can only have one time point per measure (i.e. each time point is its own measure and must be entered separately, can use the ‘Copy Outcome’ button and change time frame). In cases where a parameter is measured at several time points, but none of the time points are of particular interest (parameter being assessed over time), enter the time period instead of all of the sampling time points.

- **Eligibility**: Either copy directly from the protocol, or create a limited list useful for a potential participant to assess whether they may be eligible to enroll. To create a bulleted list, use hyphens and spaces to create a bulleted list in any free-text field.
  - For a first-level bullet: start the line with space hyphen space.
  - Indent by increasing the number of hyphens between the spaces (1 hyphen = level 1 bullet, 2 hyphens = level 2 bullet, etc.).
  - The same principle can be used to create numbered lists.

xiv. Contacts

- Overall Contacts: Confirm this information with the Study Team [or list central contact information here if Institution / Department offers this, common in Cancer Centers] Note: either a Central Contact *or* Facility (Location) Contacts are required; in general, a central contact is used when a central contact will coordinate enrollment across several institutions.
    - Contact information is displayed on the public site if the overall recruitment status is set to either 'Not Yet Recruiting' or 'Recruiting'
- Overall Study Officials: Principal Investigator of the overall trial; more than one Principal Investigator may be listed.
- Location:
    - Facility: [institution]
    - First/Last: [contact] Note: either a Central Contact *or* Facility (Location) Contacts are required; if using Facility but not Central contacts, a contact must be provided for each Facility
    - Phone: [contact]
    - Email: [contact]
    - Investigators: Local Site Principal Investigator or Sub-Investigator
        i. Note: If this is a multi-site IIT, there will be an overall study PI and a local PI. If the study is open only locally, the study PI is often the same as the local PI

xv. Plan to Share IPD: select 'No' if there is no plan to share deidentified individual participant-level data with other researchers after the study is completed, or if the PI is undecided about whether IPD will be shared. Select Yes if there *is* a plan [Link to institutional template language / policy here]. If you select "No", you will need to provide a reason why IPD cannot/will not be shared (can simply be "there are no plans to share IPD"). Refer to the "CTRR IPD (Data) Statement Tool March 2019" available in the Taskforce Dropbox. Plan Description

- What supporting information will be available
- Time Frame
- Access Criteria
- URL to additional information

xvi. References: [as relevant]

- Links: [link to lab or study page here, as relevant]
- Description: [as relevant]

5. **Check Spelling:** From the Record Summary Page, Click on ‘Spelling’ at the top of the Protocol Section. This will highlight errors and any unexpanded acronyms to correct prior to sharing a draft with the Study Team.
6. **Seek Approval & Release for Review:** Email Study Team with any final queries and attach a PRS Draft Receipt of the ClinicalTrials.gov Registration Record for their review (in case they are unfamiliar with the PRS System and/or do not have access to view the study record). This may be an iterative process. Incorporate any edits and once approval is received, release the record for PRS Review.
    a. With Investigator (or their delegate) approval, the [PRS Administrator] releases the record for PRS Review
    b. The ClinicalTrials.gov PRS office will review the study record after it is released (submitted) and before it is published to ClinicalTrials.gov. This review usually takes 2-5 business days for registration submissions (may take longer) and focuses on apparent validity (when possible), meaningful entries, logic and internal consistency, and formatting. Following the review, the reviewer will either
        i. Assign an NCT number and the information will be posted to the ClinicalTrials.gov public site, or
        ii. Respond with comments that must be addressed as “Corrections"
            - The [PRS Administrator] recommends changes to the Study Team, incorporating any feedback they may provide, and once approval is received from the Study Team re-releases the record for another round of ClinicalTrials.gov QC review.

- "Corrections" for registration QC comments must be submitted within 15 calendar days

7. **Notify Study Team of NCT Number and Next Steps**: After the study is registered to ClinicalTrials.gov, the [PRS Administrator] emails the Study Team's POC to:
    a. Notify Study Team that NCT number is assigned and where to enter it into [CTMS]. [consider link to Service Feedback Survey]
    b. If the trial is an Applicable Clinical Trial (ACT) per FDAAA, or an NIH-funded clinical trial in scope of the NIH dissemination policy, share results reporting requirements with the Study Team.
    c. For most federally funded studies, a copy of the blank ICF must be posted (on a federal website, e.g., ClinicalTrials.gov) Explain the mandate and provide direct link to OHRP website for their information. The requirement applies to studies supported by Common Rule agencies, including NIH. Any version of the blank ICF used while enrolling participants may be uploaded, only one version is needed even for multi-site trials. The must be done at any time after the trial is closed to recruitment, but no later than 60 days after the last study visit by any participant.

Glossary

- **ACT:** Applicable Clinical Trial
- **CMS:** Centers for Medicare and Medicaid Services
- **FDA**: Food and Drug Administration, federal agency of the US Department of Health and Human Services.
- **FDAAA**: Food and Drug Administration Amendments Act
- **ICMJE**: International Committee of Medical Journal Editors (http://www.icmje.org/)
- **IIT**: Investigator-Initiated Trial. Often determined using OnCore's PC Console > Main > Investigator Initiated Protocol.
- **IPD**: Individual Participant Data
- **IRB:** Institutional Review Board

- **NCT**: National Clinical Trial, the NCT number is assigned by ClinicalTrials.gov upon acceptance of the registration record
- **NIH**: National Institutes of Health
- **OHRP:** Office for Human and Research Protections
- **PI:** Principal Investigator
- **PM:** Program Manager
- **POC:** Point of Contact
- **PRMC**: Protocol Review and Monitoring Committee
- **PRS:** Protocol Registration and Results System
- **Study Team**: This is the research group that includes the PI, study coordinators, and program managers per the IRB application
- **SOP:** Standard Operating Procedure

Document History:

- 28 April 2021: Initial Draft written by Meredith Rhodes, UW-Madison
- 12 September 2021: Review by Alyssa Savadelis, Case Comprehensive Cancer Center
- 24 November 2021: Review by Sarah Snider, MUSC
- 11 March 2022: Review by Scott Patton, Stanford University
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