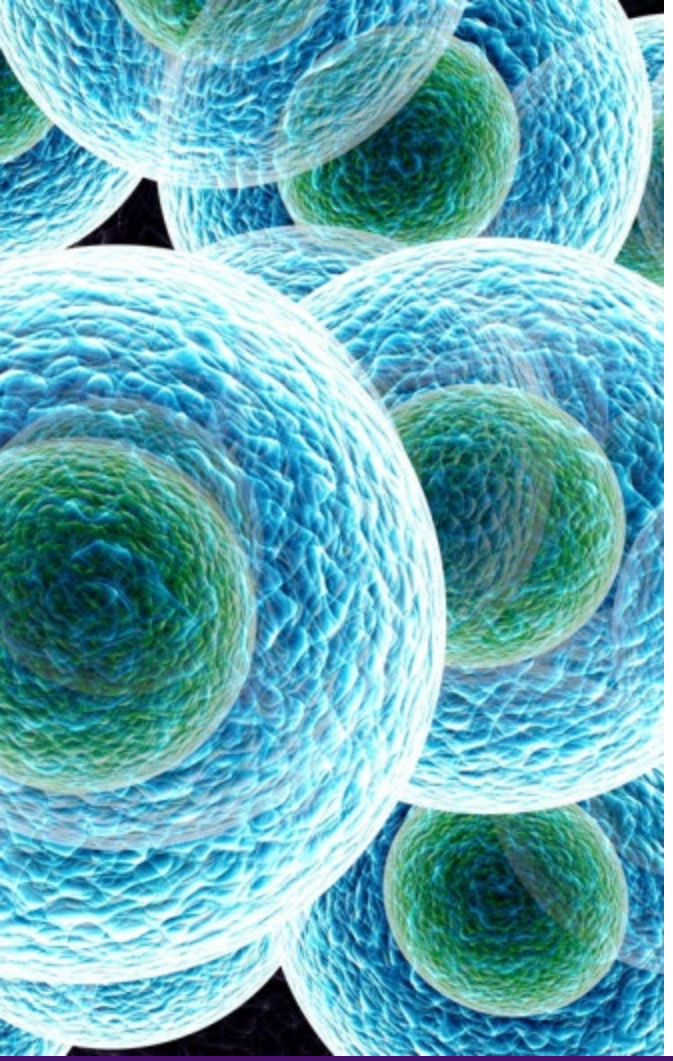

DAIDS CRSS ClinicalTrials.gov Initial Registration Process

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Agenda

1. General Overview of ClinicalTrials.gov and ClinicalTrials.gov PRS
2. ClinicalTrials.gov PRS Definitions
3. Workflow of an Initial Registration (Includes Timelines and Levels of Review)
4. Endpoints and How to Enter them in CT.gov
5. Common Issues and How to Avoid Them
6. Questions – Who to contact

General Overview of ClinicalTrials.gov and ClinicalTrials.gov PRS

Presented by: Sara McCarthy

ClinicalTrials.gov (CT.gov)

- CT.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. Studies are generally submitted to the Website (that is, registered) when they begin, and the information on the site is updated throughout the study. Results of the study are submitted after the study ends.

- Sponsors must use ClinicalTrials.gov to fulfill the requirements of FDAAA 801 (PDF).

- CT.gov requirement states that any updated information must be submit ed only when an IRB/EC approval is obtained on the updated protocol.

- The regulations at 42 CFR 11.24(a) require that the responsible party register an applicable clinical trial **not later than 21 calendar days after enrolling the first human subject**
  - This requirement is met once the record is initially submitted

ClinicalTrials.gov PRS

- Draft records are submitted through the ClinicalTrials.gov Protocol Registration and Results System (PRS).
  - Initial registration is completed by the PPD Team through ClinicalTrials.gov PRS.
  - The registration process is triggered when the PPD Team receives a specific email requesting initial registration take place.

- A PRS administrator completes a review of the record and provides feedback within the CT.gov PRS.
  - Feedback can include:
    - Major Issues (items that are mandatory to revise)
    - Advisory Issues (not mandatory to revise, suggestions from reviewer to improve record)

- There are multiple PRS administrator reviewers and there is no way to control/request which reviewer reviews a protocol record.

ClinicalTrials.gov PRS Definitions

Presented by: Payton Pearson

ClinicalTrials.gov PRS Definitions

- **Brief Title**
  - A short title of the clinical study written in language intended for the lay public. The title should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.
    Text Box Limit: 300 characters.

- **Acronym**
  - An acronym or abbreviation used publicly to identify the clinical study, if any.
    Text Box Limit: 14 characters.

- **Official Title**
  - The title of the clinical study, corresponding to the title of the protocol.
    Text Box Limit: 600 characters.

ClinicalTrials.gov PRS Definitions

- **Overall Recruitment Status**
  - Not yet recruiting: Participants are not yet being recruited
  - Recruiting: Participants are currently being recruited, whether or not any participants have yet been enrolled
  - Enrolling by invitation: Participants are being (or will be) selected from a predetermined population
  - Active, not recruiting: Study is continuing, meaning participants are receiving an intervention or being examined, but new participants are not currently being recruited or enrolled
  - Completed: The study has concluded normally; participants are no longer receiving an intervention or being examined (that is, last participant's last visit has occurred)
  - Suspended: Study halted prematurely but potentially will resume
  - Terminated: Study halted prematurely and will not resume; participants are no longer being examined or receiving intervention
  - Withdrawn: Study halted prematurely, prior to enrollment of first participant

ClinicalTrials.gov PRS Definitions

- **Dates**
  - Study Start Date (SSD):
    - Anticipated = Estimated date on which the clinical study will be open for recruitment of participants
    - Actual = Actual date on which the first participant was enrolled
  - Primary Completion Date (PCD):
    - Anticipated = Estimated 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 study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcomes.
    - Actual = Clinical study has reached the primary completion date; date must be updated to reflect the actual primary completion date.

ClinicalTrials.gov PRS Definitions

- **Dates** (continued)
  - Study Completion Date (SCD):
    - Anticipated = Estimated date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.
    - Actual = Clinical study has reached the study completion date; date must be updated to reflect the actual study completion date.

ClinicalTrials.gov PRS Definitions

- **Brief Summary**
  - A short description of the clinical study, including a brief statement of the clinical study's hypothesis, written in language intended for the lay public.
    Text Box Limit: 5000 characters.

- **Detailed Description (Not Required)**
  - Extended description of the protocol, including more technical information (as compared to the Brief Summary), if desired. Do not include the entire protocol; do not duplicate information recorded in other data elements, such as Eligibility Criteria or outcome measures.
    Text Box Limit: 32,000 characters.

Workflow of an Initial Registration

Presented by: Sara McCarthy

Workflow of an Initial Registration

1. PPD receives a notification to write a draft record **via email from the study team (Medical Officer (MO)/Network Point of Contact (POC))** sent to PPD NARACTgov shared mailbox (naractgov.sm@ppd.com) and the NIH DAIDS-Trials shared mailbox (daids-trials@nih.gov)
   - Email MUST CONTAIN AS ATTACHMENTS: Completed CT.gov checklist, copy of final protocol and the final Site Assignment Memo.
     - NOTE: The site assignment memo must contain the site name, address and site contact name, phone number and email.
   - Optional attachment: IRB approval letter (if available at time of request)

2. PPD Reg Affairs Specialist creates the draft record and may request additional information from the Network POC and/or MO. Draft is sent to the requestor within 2 weeks of initial email receipt. (Timeline: 2 weeks [10 business days])

Workflow of an Initial Registration

3. MO/Network POC reviews the draft record and supplies comments back to PPD NARACTgov shared mailbox and the NIH DAIDS-Trials shared mailbox (Timeline: 5 business days)

4. PPD Regulatory Affairs Specialist incorporates edits (if applicable) and returns the revised second draft to the MO/Network POC for secondary review (Timeline: 2 business days)

5. Discussions with the MO/Network POC about the content of the record continue until they approve the record for release.

6. PPD Reg Affairs Specialist will approve and release the record in CT.gov PRS system for the PRS Admin review (Timeline: Within 1 business day of receipt of approval to release)

Workflow of an Initial Registration

7. CT.gov PRS Admin team returns the draft record to PPD with comments/feedback if they have changes, they want to be made. (Timeline: Comment/feedback from PRS typically takes 2-5 business days.)

8. PPD sends MO/Network POC second draft containing the PRS Admin comments. (Timeline: 2 business days from receipt of comments)

9. MO/Network POC reviews/edits/comments and approves sending the second draft record to CT.gov PRS Admin for review and PPD releases the revised record for PRS Admin review.
   + The above steps (#7-9), will repeat until the record is approved by CT.gov PRS Admin team.

Workflow of an Initial Registration

10. Once the record is approved by the PRS Admin team with no further comments/feedback, an NCT number is assigned, and the record is posted publicly to CT.gov.
    - The public website listing is an automated process and takes 2 business days for the record to appear. There is no way to speed up this timeline.

+ **Total timelines from initial request to NCT number assignment will vary if there are multiple rounds of reviews/edits by the requestor prior to release, or by PRS prior to approval.**

PRS Review Process Important Information

- Once the record is released to the PRS review administrators, it is out of PPD's hands, and we do not control the review process.

- PRS reviewers are randomly assigned and PPD does not have a contact name.
  - PPD only sees "PRS Reviewer #" in communications and when communicating with the reviewer, it is through a general email: register@clinicaltrials.gov

- PRS reviewers are assigned after each release which means that multiple reviewers may review one record if comments were received and then addressed.

Initial Registration Email Requirements

- Email recipients: naractgov.sm@ppd.com AND daids-trials@nih.gov
- Title of email: DAIDS CRSS Initial Registration Request: [Insert Protocol Number] (Example: DAIDS CRSS Initial Registration Request: X1234)
- Required attachments:
  - Completed CT.gov checklist
  - Copy of final protocol
  - Final Site Assignment Memo - must contain the site name, address and site contact name, phone number and email.
- Optional attachment:
  - IRB approval letter (if available at the time of request)

Initial Registration Email Requirements

- Additional information to be included in body of email:
  - Name and email address of the Network POC who will be the point of contact during the review process and who will provide approval of the draft record for release
  - Anticipated Study Start Date
  - Anticipated Primary Completion Date
  - Anticipated Study Completion Date

Initial Registration Email

The initial registration process is triggered by the study team member (DAIDS Medical Officer [MO] or Network Point of Contact [Network POC, a person who can review and approve the submission]) sending an email to naractgov.sm@ppd.com with daids-trials@nih.gov in copy requesting that a protocol be registered.

This email is the ONLY way the PPD team will be alerted that a protocol is ready for CT.gov registration and begin the registration process.

+ Please note that copying PPD on emails, such a Full Regulatory Review email, **does not** constitute a request for registration.

Endpoints and How to Enter them in CT.gov

Presented by: Payton Pearson

Endpoints and How to Enter them into CT.gov

- **For each primary and secondary outcome measure:**
  - Name of the specific outcome measure, including any categories in which outcome measure data are aggregated
  - Description of the metric used to characterize the specific outcome measure
  - Time points at which the measurement was assessed
  - Results are due exactly 1 year after the Study Completion Date (SCD)
  - Results must be entered as a whole, wait until everything is collected to enter if a study has multiple parts

Endpoints and How to Enter them into CT.gov

- Be mindful of character limits on outcome titles and descriptions
  - The outcome measure must be brief but cover everything that will be measured
  - For best practice, use multiple outcome measures to report results for the same measure at different time points
- The wording must be precise and adhere to the PRS format
  - Allows for accurate reporting of the analysis population
- Timeframes must be specific and sometimes are not easily found in the protocol
- Measures must be split up and cannot contain more than one variable
- This topic is where most of the back and forth on finalizing a record takes place

Common Issues and How to Avoid Them

Presented by: Payton Pearson

Common Issues Seen

- **PRS Validation Rules**
  - ERROR – Written in RED and indicates a serious issue that must be addressed (Missing content, internal inconsistency)
  - WARNING – Potentially serious issues that should be reviewed and addressed as needed (Study start date data element)
  - NOTE – Written in Blue and indicates potential issues that should be reviewed and addressed, as needed (May be ignored)

  - **Review Comments**
    - Two types of comments
      - Major – Must be addressed
      - Advisory – Suggestions to improve the clarity of the record

Common Issues Seen

+ Outcome measures that include too many variables

+ Outcome measures should not be copied directly from protocol

+ Timeframes must be specific

+ Anticipated dates cannot be in the past

+ National Institute of Allergy and Infectious Diseases Clinical Research Management System (NIAID CRMS) discrepancy

+ For the overall Study Status to be updated to “Recruiting”, there must be at least one site with the site status of “Recruiting”

How to Avoid Common Issues

- **Outcome measures that include too many variables**
  - Some measures may need to be split up
    - The Outcome Measure describes multiple assessments with potentially DIFFERENT UNITS OF MEASURE. Assessments with different Units of Measure (e.g., weight and height) must be presented in separate Outcome Measures. Please revise to present these assessments in separate Outcome Measures (e.g., weight in kilograms, height in meters), as appropriate, or to clarify how multiple measurements will be aggregated to arrive at one reported value (e.g., weight and height will be combined to report Body Mass Index (BMI) in kg/m^2).
    - Assessments using unique measurements (e.g., Visual Analog Score for pain, Physicians Global Assessment to measure quality of life) that share a common Unit of Measure (e.g., Units on a Scale) should be presented as separate Outcome Measures
- **Outcome measures should not be copied directly from protocol**
  - PRS has specific wording that they like to use

    The measure does not appear to include sufficient information to understand what will be assessed. The phrases "Pharmacokinetic (PK) profile/parameters" and "Pharmacodynamic (PD) profile/parameters" do not specify what will be assessed or measured, and they imply that more than one measure will be collected as pharmacokinetic/pharmacodynamic data. Please revise the Outcome Measure Title to clearly state what will be measured and reported. Also, enter each assessment separately, so only one measure is included in each Outcome Measure Title (e.g., Maximum Plasma Concentration [Cmax]). Can you provide the specifics on what is being assessed? Cmax?

How to Avoid Common Issues Continued

- **Timeframes must be specific**
  - **The Time Frame does not appear specific or in the correct format.**
  - The Time Frame provided is not specific. The Time Frame should indicate the specific time point(s) at which the outcome measure will be assessed and for which data will be reported. Please see acceptable examples below:
    - "baseline, pre-intervention/procedure/surgery"
    - "during the intervention/procedure/surgery"
    - "immediately after the intervention/procedure/surgery"
    - "1 year, year 1"
    - "up to 24 weeks"

- **Anticipated dates cannot be in the past**
  - Anticipated dates must be in the future with enough time to account for PRS approval
  - If more time is needed to account for results reporting, extend the PCD and SCD/ask for a results extension **PRIOR** to the SCD 1-year anniversary expiring

How to Avoid Common Issues Continued

- NIAID CRMS Discrepancy
  - Data within CRMS needs to be accurate as we verify information there to complete the weekly report updates
  - Having incorrect data delays release of records because we then must reach out to the study team to verify (study status, start date)

Questions?

Any questions related to the CT.gov Initial Registration process should be directed to naractgov.sm@ppd.com and daids-trials@nih.gov.

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