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Identifying and Managing Compliance for Clinical Trials Involving Cornell Research with Human Subjects

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This document is intended to help researchers at Cornell's Ithaca-based campuses understand when their research could be considered a "Clinical Trial", communicate special responsibilities that principle investigators (PIs) must fulfill for some clinical trials, and provide guidance on how PIs can meet these special obligations.

I. An expanded definition: What is a "clinical trial"?

The NIH definition

On January 25, 2015, the National Institutes of Health (NIH) published a revised and expanded interpretation of the term "clinical trial", with the aim of improving the dissemination of research and encouraging transparency in these critical experiments. As redefined by NIH, the term is no longer limited to clinical studies that seek to develop treatment for a medical condition, and now includes some non-clinical, biomedical, and social behavioral research interventions[1]. NIH has now added new requirements for research that meets this expanded definition. More Cornell studies could now be considered clinical trials, and the PIs for these studies must comply with additional obligations.

The Common Rule definition

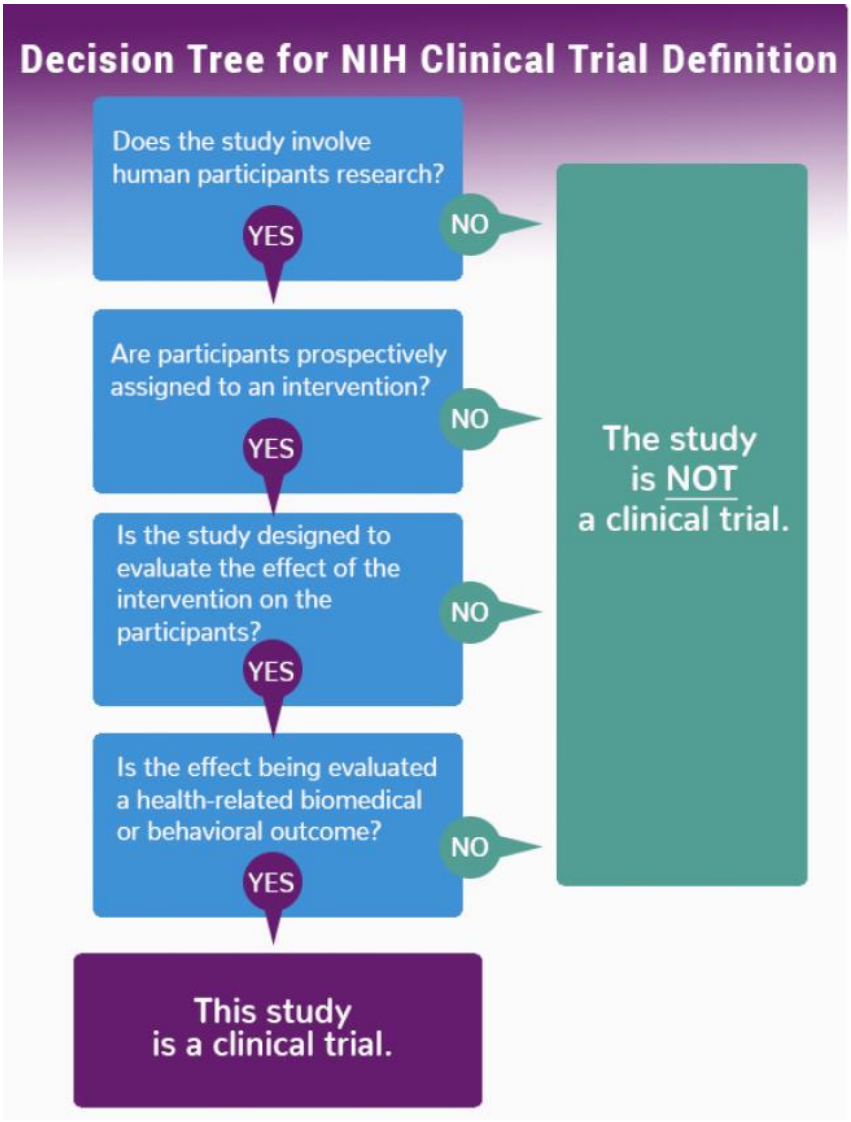
While the NIH definition only affects research funded by, or for which funding is sought from, NIH, the implications are much broader. The expanded NIH definition of "clinical trial" appears verbatim in the revised version of the "Common Rule", the major federal regulation governing research with human subjects, which becomes effective on January 21, 2019. Previously, the Common Rule did not include a definition of clinical trial. As described below, for federally-

[1] In July 2018, the NIH announced that it would delay enforcement of its expanded clinical trial definition for basic science studies until September 24, 2019, during which time the NIH "will assess its approach to registration and reporting for these studies and seek feedback from the research community on its registration and reporting requirement for these studies." Nevertheless, until the future of the NIH definition is clear, the IRB staff advises researchers to proceed as if the policy is in effect. Please contact the IRB if you have questions.

funded research that meets the Common Rule definition of a clinical trial, PIs must comply with a new compliance obligation.

II. How will I know if my study is a clinical trial?

<u>If answers to the NIH decision tree below are all "yes", your study is a clinical trial.</u>



<u>Note</u>: The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.

Both NIH policy and the Common Rule define a clinical trial as: "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes." This definition must be considered in connection with a long list of case studies issued by NIH (and which they continue to revise) that add nuance. The NIH website includes case studies, FAQs, and a decision tool to help researchers understand the new definition, but it remains confusing to apply. If you are uncertain about whether or not your study is a clinical trial, please contact the IRB for assistance.

The newly redesigned IRB application form contains prompts to enable staff to determine whether a study might be a clinical trial. The IRB approval letter will specify that a study is a clinical trial when the staff have determined that this is the case. These approval letters include a brief summary of actions that PIs either must take, or are strongly encouraged to take, depending on the funding status of the research.

For researchers seeking NIH funding for human participant research, the PI must determine at the proposal stage whether or not their proposed project will be defined as a clinical trial, in order to apply for the appropriate funding opportunity.

III. What do I need to do if my study is a clinical trial?

If your study is a clinical trial you as the researcher are ultimately responsible for complying with applicable obligations, as summarized below:

NIH funding: If you are a PI who has or is seeking NIH funding for a clinical trial, you are responsible for meeting the following additional compliance obligations:

Apply for the correct FOA[2]: Certain NIH Funding Opportunity Announcements (FOAs) are applicable only to clinical trials or non-clinical trials. Applying for the wrong FOA may make your submission ineligible for funding.

Registration and reporting on ClinicalTrials.gov: Clinical trials in competing applications and contract proposals submitted on or after January 18, 2017 must register, submit updates throughout the project, and post results information on ClinicalTrials.gov. Compliance with this requirement is expected to require a significant dedication of time and effort throughout the study.

[2] NIH has instituted a period of leniency for applications submitted to the incorrect FOA based on study-type designation (e.g., clinical trials required, clinical trials optional, clinical trials not allowed). NIH will not administratively reject any applications submitted to an incorrect study-type FOA, and applications will be reviewed based on the review criteria of the FOA to which they are submitted.

Training in Good Clinical Practices (GCP): Starting January 1, 2017, those involved in the design, conduct, oversight, or management of a clinical trial must be trained in GCP. For NIH-funded clinical trials, as a condition of protocol approval, the Cornell IRB will require evidence that all study personnel listed on the protocol have completed GCP training within the last 3 years. NIH does not require a specific course. Cornell researchers may complete GCP training online through CITI (Collaborative Institutional Training Initiative). Note that this training is in addition to basic IRB human subjects training required for researchers on expedited and full board review studies.

Consent form posting: This requirement is described below.

All federal funding: For clinical trials supported by any type of federal funding (NIH, NSF, DOD, etc.), the PI is responsible for the following additional compliance obligation:

- Consent form posting: The PI must post a copy of an IRB-approved consent form used for enrollment purposes to ClinicalTrials.gov after the study is closed to recruitment, but not later than 60 days after the last study visit by any subject. Please note that the IRB office will not be able to remind PIs to fulfill this obligation in a timely manner.

All other projects: Regardless of the funding status or source for your human subjects work, the Cornell IRB strongly recommends that you choose to follow the compliance practices required by NIH as a best practice. Publication in certain journals could be jeopardized if researchers choose not to comply with these best practices.

CLINICALTRIALS.GOV SYSTEM

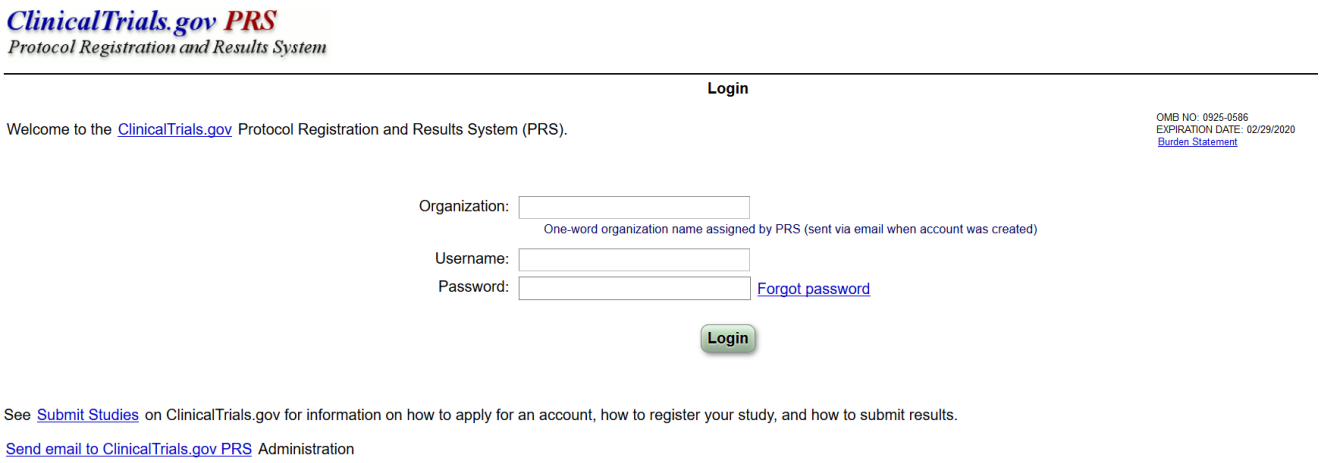
As described in section III, above, for NIH-funded clinical trials, registration and results posting on ClinicalTrials.gov is required. Likewise, for clinical trials supported by any type of federal funding, the PI is required, under the newly revised Common Rule, to post a copy of the consent form to ClinicalTrialsgov. ClinicalTrials.gov is a publicly available registry and results database website of federally and privately supported clinical trials conducted in the United States and abroad. The purpose is public disclosure of key information about clinical trials currently enrolling participants, as well as those that have been conducted in the past. This site captures summary protocol information before and during the trial, as well as summary results and adverse event information of a completed trial. Once a study has been registered on the website, the PI assumes responsibility for adhering to obligations such as yearly updates. **Unfortunately, the IRB staff is only able to provide minimal support for researchers in using ClinicalTrials.gov.**

How do I register my study on ClinicalTrials.gov?

ClinicalTrials.gov establishes one Protocol Registration and Results System (PRS) account for each organization. Cornell University's Ithaca-based campuses have one single account. As the designated "PRS Administrators", the IRB staff can add users to the organization's account.

- **New users:** If a study is a clinical trial:
  - The PI (if a new user) should request that the Cornell's PRS Administrator (IRB staff) add them as a user to the website.
  - The PRS Administrator will then create an account under Cornell's PRS, and the PI will automatically receive an email from the system with a web address and login information to create their own username/password.
  - After completion, the PI should proceed to create their clinical trial study record on the site.
  - Once the study record passes system review, an email notification will be sent with the ClinicalTrials.gov Identifier (NCT number), indicating that the study is now registered.
  - Generally, within 2 business days of registration, the system will post the record. Once registered, the study record becomes a permanent part of ClinicalTrials.gov and cannot be removed.
- **Existing users:** Researchers can create new study records or edit their existing records by logging into the system through: https://clinicaltrials.gov/ct2/manage-recs/register.
  - The system will ask a security question (e.g., day of week) to ensure the user is not a bot and the following sign-in page will appear (see screenshot below).
  - The researcher should indicate their organization account as **CornellU** and sign in with their username/password.

- Then follow the prompts to modify or create a new study record.



What study materials do I need to upload?

- **Consent forms**: Federally funded clinical trials are required to post their study consent forms to ClinicalTrials.gov after the trial is closed for recruitment within 60 days after the last study visit by any subjects.
- **Study results:** U.S. law also requires that some studies submit results to the ClinicalTrials.gov site within 1 year of the Primary Completion Date. Please check with your funder's program officer for these requirements.
- **For more information** see the Frequently Asked Questions section on the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11). Please also refer to the ClinicalTrials.gov guide, "How to Submit Your Results" (https://clinicaltrials.gov/ct2/manage-recs/how-report) for step-by-step details.

How do I manage my ClinicalTrials.gov record?

- **Keep record up to date**: PIs are responsible for creating, managing, and modifying their own study records.
    - On an annual basis, each record owner will need to log into the CT system and update any information or address any problems the system flags.
- **Record errors**: All study records must be free of ERROR messages in order to be released to the public.
    - If the system identifies an error, the record is deemed a "problem record". The site will then flag the record and send an auto-email to the PI indicating that their record needs attention, along with instructions on how to log in to address the problem.

- The Cornell PRS Administrator will also be notified of PIs who have received this email and will follow up with them to ensure they have addressed the issues, or address any questions they may have about the system.
- The site has a robust Customer Support Team available to assist with any issues that go beyond PRS Administrator capability.

How do I reconcile a "problem record"?

To see which error types apply to your specific record, log in through https://clinicaltrials.gov/ct2/manage-recs/register, indicate '**CornellU**' as your organization, and sign in with your username/password.

- **Problem records** typically fall under the following "problem types":
  - *Not Recently Updated*
  - *Record Has Error*
  - *Update Not Released/Entry Not Completed*
  - *PRS Review Comments*
  - *Missing FDAAA Information*
  - *Late Results – per FDAAA*
  - *Incomplete Results – per FDAAA*
  - *Never Released*
- **Example of a "problem record"** could be an issue with recruiting status (e.g., date expired), specific information needs to be verified (e.g., a study location), or inaccurate PI contact information.
  - Problem types for each record will display in red in the right-hand column.
  - If more than one problem type applies, the PI should make all changes to the study record before hitting the green "Entry Complete" button to signal they are done making edits. This will allow all changes to the record to be publicly posted on ClinicalTrials.gov at one time.
  - The PRS Administrators may also need to review, approve, and "release" all completed records once PIs addresses their issues.
  - Please note that some data elements may require more rapid updates, until the study is completed.