Resource Document for UMass Researchers/Staff to Comply with the NIH Revision to the Definition of a Clinical Trial

Office of Research Compliance

University of Massachusetts, Amherst

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A. Revised NIH Definition of Clinical Trial

Website: https://grants.nih.gov/policy/clinical-trials/definition.htm

Notice/Policy: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html

A **research study**[1] in which one or more **human subjects**[2] are prospectively **assigned**[3] to one or more **interventions**[4] (which may include placebo or other control) to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes.**[5]

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[1] See Common Rule definition of *research* at 45 CFR 46.102(d).

[2] See Common Rule definition of *human subject* at 45 CFR 46.102(f).

[3] 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.

[4] 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. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

[5] *Health-related biomedical or behavioral outcome* is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

B. Determination If Your Human Subject's Research Study Meets the Revised NIH Definition of a Clinical Trial?
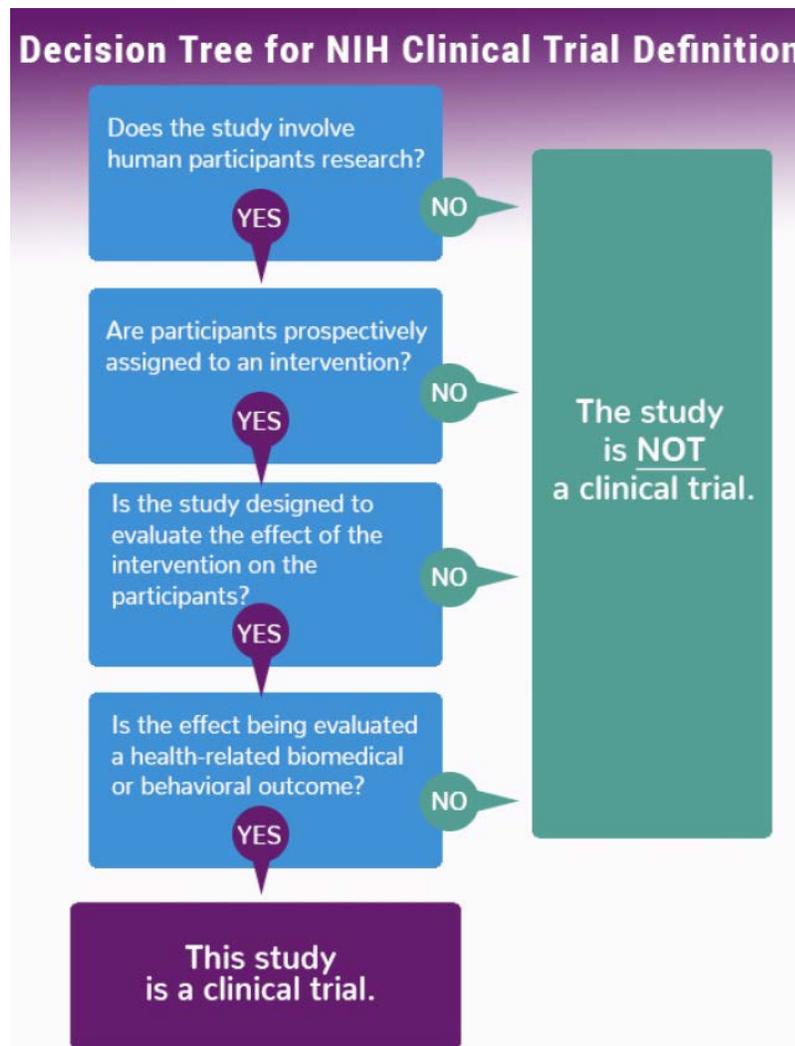
Please use resources below to make this determination or contact the Human Research Protection Office at 413-545-3428 or email at humansubjects@ora.umass.edu **:**

https://grants.nih.gov/ct-decision/index.htm

https://grants.nih.gov/policy/clinical-trials/CT-decision-tree.pdf

https://grants.nih.gov/grants/policy/faq_clinical_trial_definition.htm

https://grants.nih.gov/policy/clinical-trials/case-studies.htm

C. NIH Policies for Data and Safety Monitoring of Clinical Trials

Notice/Policy: https://humansubjects.nih.gov/data_safety

Note: If your study involves a clinical trial you must include a Data and Safety Monitoring Plan (DSMP) commensurate with the risk of your study.

Note: This plan needs to be approved by the IRB prior to enrolment of any Human Subjects.

Data and Safety Monitoring Plan Writing Guidance: (https://www.nimh.nih.gov/funding/clinical-research/data-and-safety-monitoring-plan-writing-guidance.shtml)

A DSMP should include a general description of a plan establishing the overall framework for the oversight and monitoring of a study. When formulating the Data Safety Monitoring Plan (DSMP), the PI, and the study team should consider the protocol, phase, intervention(s), target population, subject safety and privacy, risks and benefits involved in the study, data integrity and confidentiality, study coordination, and how the team will address each of these elements. When modifications to the DSMP are made before the trial begins (e.g., in response to the peer review or IRB review), a final IRB-approved monitoring plan must be submitted to the National Institute of Mental Health (NIMH) Program Officer (PO) prior to the commencement of human subjects activities. The minimum required DSMP content should include the following elements.

Note: If these elements are noted elsewhere in the application or proposal, they need not be repeated but should be referenced in the DSMP section**:**

1. Summary of the Protocol:
    o   A brief description of the study design (e.g., interventions , procedures, tests and scans, biospecimen collection, interviews and focus groups, study visits)
    o   Primary and secondary outcome measures/endpoints
    o   Sample size and target population
    o   Inclusion/exclusion criteria and how the criteria will be evaluated
    o   For multi-site trials, a list of proposed participating clinical sites and data coordinating centers and a description of each site's role
2. Roles and Responsibilities (Note this must be listed in DSMP section):
    o   Identification and description of individuals responsible for monitoring the trial (e.g., PI, Independent Safety Monitor (ISM), DSMB), their roles, qualifications, and the frequency of the monitoring activities. If the monitoring entity is an ISM or a DSMB, provide the NIMH PO and Office of Clinical Research (OCR) review with a list of the proposed membership and assurances to ensure that there are no conflicts of interest with the study team or proposed institutions.
3. Trial Safety:
    o   Description of any specific events that would preclude a participant from continuing the intervention
    o   Description of any procedures in place for managing any medication related issues (e.g., medication washout, allergic reactions, drug interactions, discontinuation/stoppage of medication, use of rescue mediations)
    o   Description of the potential risks and the measures in place to protect participants against foreseeable risks

- o Description of the consent/assent procedures (e.g., by whom, how and under what conditions will a subject be consented)
- o Description of the mechanisms in place to protect subject privacy (e.g., interviews will take place in a private room, whether results of testing data will be shared with participant's legally authorized representative, privacy for minors, secure means of communication between investigators and participant, e.g., telephone, web portal)
- o Description of the trial stopping rules for the study, if any (e.g., increased suicidal ideation, greater than expected morbidity or mortality rate)
- o Description of the plan for management of incidental findings (e.g., a brain tumor or potential structural abnormality discovered during a scan)
- o Description of the process for the disclosure of any conflicts of interest that may potentially challenge participant safety or bias the data and how the conflict will be managed
- o For multi-center studies, a description of the procedures for ensuring compliance with the monitoring plan including requirements for data reporting across study sites
- o Description of the data security in place to protect the confidentiality of the data (e.g., password protected encrypted electronic records) and any limits to confidentiality (e.g., suicidal ideation, child abuse)

4. Reportable Events:
   - o Description of the process and timelines (e.g., hours, days) for collecting and reporting Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Problems Involving Risks to Subjects or Others to appropriate monitoring and regulatory entities (See NIMH Reportable Events Policy for definitions and timeframes)
   - o Specific plan and timeframe for reporting IRB and/or ISM/DSMB actions to the NIMH (e.g., protocol violations, non-compliance, suspensions, terminations)

5. Data Management, Analysis, and Quality Assurance:
   - o Identification of data sources (e.g., questionnaires, medical records, biospecimen collections, audio/video recordings)
   - o Description of the security measures in place to protect data sources including how the data will be labeled and stored
   - o Quality assurance measures for subject recruitment, enrollment, enrollment targets, and for the validity and integrity of the data. E6 Good Clinical Practice (R1): 1.46 defines quality assurance as "All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)"

If your study involves an NIH-defined Phase III or multisite clinical trial your DSMP must include a Data and Safety Monitoring Board.

Policy Governing Independent Safety Monitors and Independent Data and Safety Monitoring Boards is available at the following link:
https://www.nimh.nih.gov/funding/clinical-research/policy-governing-independent-safety-monitors-and-independent-data-and-safety-monitoring-boards.shtml

If you have any questions, please contact the Human Research Protection Office at 413-545-3428 or email at humansubjects@ora.umass.edu

D. Good Clinical Practice (GCP) Training

The principles of Good Clinical Practice (GCP) help assure the safety, integrity, and quality of clinical trials by addressing elements related to the design, conduct, and reporting of clinical trials. GCP training describes the responsibilities of investigators, sponsors, monitors, and IRBs in the conduct of clinical trials.

GCP training aims to ensure that:

- the rights, safety, and well-being of human subjects are protected
- clinical trials are conducted in accordance with approved plans with rigor and integrity
- data derived from clinical trials are reliable

The policy applies to NIH-funded clinical investigators and clinical trial staff who are responsible for the design, conduct, oversight, or management of clinical trials. The policy describes the investigator as the individual responsible for the design and conduct of the clinical trial at a trial site or, if a team of individuals at a trial site are involved, the investigator leading the team. The policy describes clinical trial staff as those who are responsible for study coordination, data collection, and data management.

Website: **https://grants.nih.gov/policy/clinical-trials/good-clinical-training.htm**

Notice/Policy: **https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-148.html**

Frequently Asked Questions:
https://grants.nih.gov/grants/policy/faq_nih_good_clinical_practice.htm#5157

Note: The policy applies to all active NIH grants and contracts, no matter what point they are in the life cycle of the trial. This policy is effective January 1, 2017
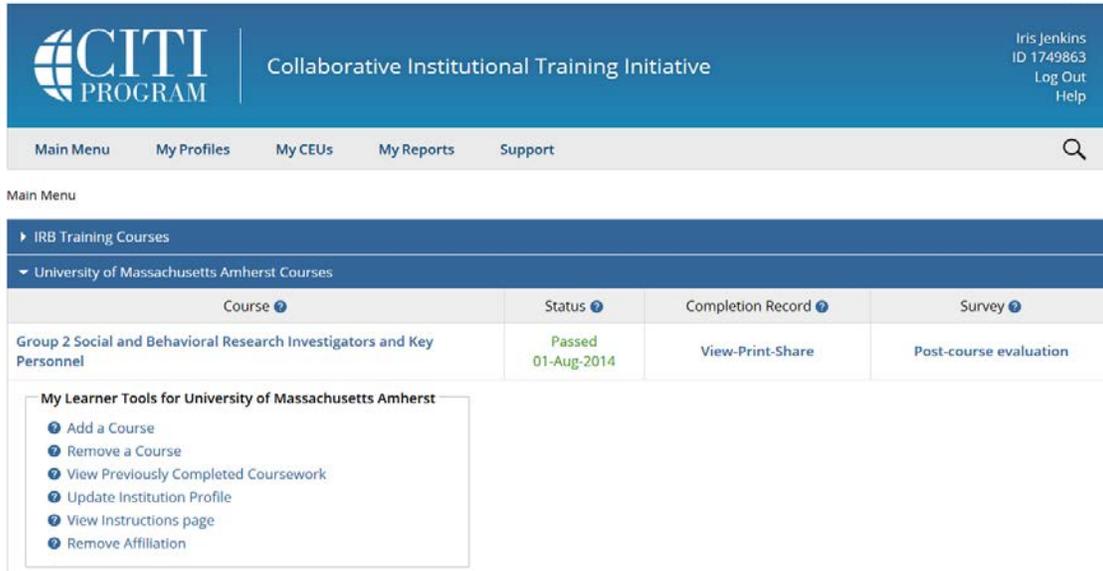
Course available through CITI

FAQs: https://grants.nih.gov/grants/policy/faq_nih_good_clinical_practice.htm#5163

The NIH GCP training policy is part of a multi-faceted NIH initiative to enhance the quality, relevance, feasibility, efficiency, and transparency of NIH funded clinical trials through stewardship reforms (see Hudson KL, Lauer MS, Collins, FS. Toward a New Era of Trust and Transparency in Clinical Trials. JAMA. 2016; 316(13):1353-1354). The principles of GCP help assure the safety, integrity, and quality of clinical trials. GCP provides a standard for ensuring clinical trial compliance, implementation, data collection, monitoring, and reporting (e.g., safety data, accrual reports, study status, protocol deviations, unanticipated problems, or final data), and outline the responsibilities of Institutional Review Boards (IRBs), investigators, sponsors and monitors. GCP addresses elements related to the design, conduct and reporting (e.g., safety data, accrual reports, study status, protocol deviations, unanticipated problems, or final data) of clinical trials.
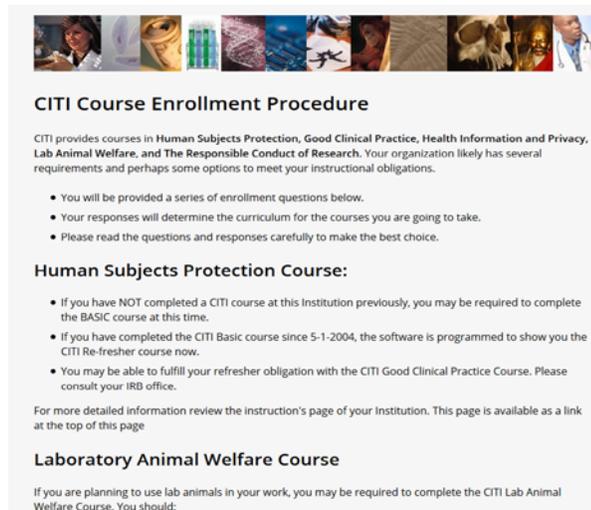
Steps to Complete the GCP training through CITI

1. *Log into your CITI Account (https://about.citiprogram.org/en/homepage/)*

2. Click "Add a Course"

3. *You will see the page below.*

4. *Scroll down to answer the Human Subjects Questions:*

Question 1

Human Subjects Research

Select the group appropriate to your research activities in the Human Subjects Research. You will be enrolled in the Basic Course for that group.
Choose one answer

○ Group 1: Biomedical Research Investigators and Key Personnel

○ Group 2: Social and Behavioral Research Investigators and Key Personnel

○ view all citi modules: This is a "DEMO" Group. If you are enrolled in the CITI program to fulfill an instructional requirement, enroll in group 1. or Group 2. above.

○ Group 3: Good Clinical Practice (GCP) This is a 12 module course in GCP and ICH-E6. This course should not be attempted until after the Basic course has been completed.

○ None of the above: I'm interested in the Lab Animal Welfare Skip questions 1 & 2 and go to Question 3.

Select "Group 3" for the Good Clinical Practice course.

5. *Answer other Questions visible on the screen. (Question #2 will need to be answered for animal users).*

6. *You will be taken back to the main screen where the GCP course will now be visible and accessible.*

E. NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

Policy: https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm

Frequently Asked Questions: https://clinicaltrials.gov/ct2/manage-recs/faq#42CFRPart11

Note: This policy is effective January 18, 2017

The NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information sets the expectation that all NIH-funded awardees and investigators conducting clinical trials will register and report results of their trial in Clinicaltrials.gov.

Both the NIH policy and the federal regulation aim to increase the availability of information to the public about clinical trials – information that is not systematically available from other public sources. The regulation and NIH policy do not affect the design or conduct of clinical trials or define what type of data should be collected during a clinical trial. Rather, they aim to help ensure that information about clinical trials and their results are made publicly available, in a timely manner, via ClinicalTrials.gov, a publicly accessible database operated by the NIH's National Library of Medicine (NLM).

Once the study has been approved by the IRB, please contact Iris Jenkins at ijenkins@ora.umass.edu or 413-577-0643 to obtain a log-in for the www.clinicaltrials.gov website.