UNIVERSITY OF SOUTHERN MAINE
Office of Research Integrity & Outreach

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AAHRPP:	Element II.3.F., & Element III.2.D.
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Procedure Title:	Registration and Maintenance of ClinicalTrials.gov

1.0 Objective

1.1. To describe the procedures, processes, and responsibilities for the registration and maintenance of a clinical trials, covered by the University of Southern Maine (USM) Human Research Protection Program (HRPP), on ClinicalTrials.gov.

1.2. To comply with consent form posting requirements of the revised Common Rule, National Institute of Health (NIH), Food and Drug Administration Amendments Act of 2007 (FDAAA), and International Committee of Medical Journal Editors (ICMJE).

2.0 General Description

2.1. The revised Common Rule requires that for any clinical trial, one consent form used in enrolling participants be posted on a publicly available Federal website within a specific time frame and ClinicalTrials.gov was identified as a website that will satisfy this requirement.

2.2. Under the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, every clinical trial funded in whole or in part by NIH is expected to be registered on ClinicalTrials.gov and have summary results information submitted and posted in a timely manner.

2.3. FDAAA requires Responsible Parties to submit clinical trial information to the Director of the NIH for inclusion in the registry and results database established via ClinicalTrials.gov.

2.4. The ICMJE requires ClinicalTrials.org registration for research projects that prospectively assign human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

3.0 Definitions

3.1. Aggregate Results means: data collected from individual-level records that have been combined for statistical or analytical purposes and that are maintained in a form that does not permit the identification of individuals.

3.2. Applicable Clinical Trial (ACT) means:

3.2.1. Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1investigations, of a product subject to FDA regulation.

3.2.2. Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric post-market surveillance.

3.3. Clinical Trial means:

3.3.1. **NIH:** 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.

3.3.2. **ICMJE:** a research project that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

3.4. ClinicalTrials.gov means: a website that provides regularly updated information about federally and privately supported clinical trial for a wide range of diseases and conditions.

3.5. Food and Drug Administration Amendment Act of 2007 (FDAAA) means: Section 801 of the federal statute, enacted September 27, 2007 that requires registration of an ACT that is initiated after September 27, 2007 or ongoing as of December 26, 2007.

3.6. Grantee means: the recipient institution of a grant or cooperative agreement from a federal agency.

3.7. International Committee of Medical Journal Editors (ICMJE) means: the group of general medical journal editors that are the authors of The Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

3.8. National Clinical Trial Number (NCT) means: A unique identifier that has been assigned to a study that has been successfully registered on ClinicalTrials.gov.

3.9. Primary Completion Date means: the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome.

3.9.1. This applies whether the clinical trial concluded according to the pre-specified protocol or was terminated.

3.10. Principal Investigator (PI) means the individual who is responsible and accountable for conducting the clinical trial.

3.11. Protocol Registration and Results System (PRS) means a web-based data entry system used to register clinical studies, provide updates, and to submit results information for registered studies.

3.12. Qualifying Trial means a clinical trial, designated by the Center for Medicare and Medicaid Services (CMS) as qualifying for coverage, as specified in the Medicare National Coverage Determination (NCD) Manual.

3.12.1. The purpose of the trial must be the evaluation of an item/service that falls within a Medicare benefit category.

3.12.2. The trial must have therapeutic intent and must enroll patients with diagnosed disease, not only healthy volunteers.

3.13. Responsible Party means the entity responsible for registering the trial and providing updated information and can be either:

3.13.1. The sponsor of the clinical trial, who is:

3.13.1.1. A person who initiates a clinical investigation, but who does not actually conduct the investigation. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated, and the employees are considered to be investigators.

3.13.2. The PI of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, provided:

3.13.2.1. The PI is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements for submitting information under this policy.

4.0 <u>Responsibility</u>

4.1. The PI of an investigator-initiated, interventional clinical trial that meets FDAAA, NIH, CMS, ClinicalTrials.gov registration and reporting requirements is responsible for posting the requisite information on ClinicalTrials.gov.

4.2. The PI of all interventional clinical studies that would like to be considered for publication within an ICMJE journal must register the clinical trials on ClinicalTrials.gov.

4.3. It is the responsibility of the Office of Research Integrity and Outreach (ORIO) staff and Institutional Official (IO) to execute this SOP.

5.0 Procedure

5.1. Determining Registration Requirements

5.1.1. The PI is responsible for determining if the study is an ACT, thus requiring registration and results information on ClinicalTrials.gov.

5.1.1.1. To determine if a study is an applicable clinical trial, please use the ACT Checklist[1] on the ClinicalTrials.gov website. https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf

5.1.2. In addition to federal requirements (42 CFR 11) and the NIH Policy, journals (i.e., ICMJE), funding sources, and insurance companies (i.e., Medicare/Medicaid) may require registration and submission of results information.

5.1.3. Studies with approved consent language stating that the study will be registered to ClinicalTrials.gov must register their study to ClinicalTrials.gov.

5.1.3.1. If it is determined that the study does not require registration per regulations and the PI decides not to register the study for publication or other purposes, then an amendment removing the ClinicalTrials.gov language must be approved by the IRB and consented subjects must be notified.

5.1.4. Studies with human subjects that are not required per regulations or publication requirements may still be registered to ClinicalTrials.gov per the PI's discretion.

5.2. Posting a Study Record

5.2.1. Determine responsible party

5.2.1.1. Studies should be registered only by the Responsible Party.
5.2.1.2. To determine who is responsible for registering a study and submitting results, please use the Elaboration of Definitions of Responsible Party and Applicable Clinical Trial[2] on the ClinicalTrials.gov website. https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

[1] https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf
[2] https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

5.2.2. Log in to PRS

5.2.2.1. You will need to log in to an account linked to the Sponsor Organization of the study you want to register.
5.2.2.2. Typically, the Sponsor Organization is the organization or person who initiates the study.
5.2.2.3. For information on obtaining a PRS account, see How to Apply for an Account[3] on the ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/manage-recs/how-apply

5.2.3. Create a new record

5.2.3.1. The person who creates the record becomes the Record Owner. All email messages about the record will be sent to this person.

5.2.4. Enter or edit study information

5.2.4.1. Provide information summarizing the study protocol, including the Brief Title, Study Type, Outcome Measures, Arms and Interventions, Eligibility Criteria, Contacts, and Study Site Locations.
5.2.4.2. See the Protocol Registration Data Element Definitions[4] https://register.clinicaltrials.gov/prs/html/definitions.html and the Expanded Access Data Element Definitions[5] https://register.clinicaltrials.gov/prs/html/expanded_access_definitions.html on the ClinicalTrials.gov website for a complete list of required and optional data elements.

5.2.5. Submit the study record for PRS Review

5.2.5.1. After all study information is entered, the person entering the information clicks on "Entry Complete."
5.2.5.2. The Responsible Party or Administrator for the study clicks on "Approve" to accept the content.
5.2.5.3. The Responsible Party or Administrator clicks on "Release" to submit the record for review by PRS Staff.
5.2.5.4. For more information about identifying the Responsible Party, see Determining Who Should Submit a Record[6] https://register.clinicaltrials.gov/prs/html/prs-users-guide.html#hdnrecord on the ClinicalTrials.gov websites.

5.2.6. PRS staff review the record

[3] https://clinicaltrials.gov/ct2/manage-recs/how-apply
[4] https://register.clinicaltrials.gov/prs/html/definitions.html
[5] https://register.clinicaltrials.gov/prs/html/expanded_access_definitions.html
[6] https://register.clinicaltrials.gov/prs/html/prs-users-guide.html#hdnrecord

5.2.6.1. After the Responsible Party releases the record, PRS Staff review it for apparent errors, deficiencies, and/or inconsistencies.
5.2.6.2. If PRS Staff find any potential issues with the record, they will add comments to the record and send an email notification.
5.2.6.3. The user must log in to PRS to view the comments.
5.2.6.4. The user then edits the study record to address the comments and resubmits the record for PRS Review.

5.2.7. Record is registered and posted

5.2.7.1. Once the study record passes PRS Review, an email notification will be sent with the ClinicalTrials.gov Identifier (NCT number), indicating that the study is registered.
5.2.7.2. Generally, within two (2) business days of registration, the system will post the record on the ClinicalTrials.gov website.
5.2.7.3. Once registered, a study record becomes a permanent part of ClinicalTrials.gov and cannot be removed.

5.2.8. Keep record up to date

5.2.8.1. The study record needs to be verified and/or updated at least once a year, with some data elements requiring more rapid updates, until the study is completed and/or the PRS Review process has concluded for submitted results information.

5.2.9. Add results

5.2.9.1. U.S. law requires some studies to submit results to ClinicalTrials.gov.
5.2.9.2. Generally, results must be submitted within one (1) year of the Primary Completion Date.
5.2.9.3. For more information, see the Frequently Asked Questions[7] on the ClinicalTrials.gov websites. https://clinicaltrials.gov/ct2/manage-recs/faq#42CFRPart11

5.3. Timeline Requirements

5.3.1. Registration

5.3.1.1. Registration must be completed no later than 21 days after the first subject is enrolled.
5.3.1.2. ICMJE requires that registration is complete prior to first subject enrollment.
5.3.1.3. A study is considered registered once the responsible party releases the record to PRS for review.

[7] https://clinicaltrials.gov/ct2/manage-recs/faq#42CFRPart11

5.3.2. Actively enrolling studies

5.3.2.1. The record of actively enrolling studies must be updated or verified every six (6) months.
5.3.2.2. The record must be verified even if no changes need to be made.

5.3.3. Informed Consent forms

5.3.3.1. 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.
5.3.3.1.1. Written materials must describe the process to request from the Federal funding agency an exception to the requirement to post the consent document, and the process to redact confidential commercial information from the consent form.

5.3.4. Studies closed to enrollment or pending results

5.3.4.1. The record of studies closed to enrollment or pending results must be updated or verified annually.
5.3.4.2. The record must be verified even if no changes need to be made.

5.3.5. Change in study status

5.3.5.1. A record must be updated within 30 days of a status change.

5.3.6. Results submission

5.3.6.1. Results must be submitted no later than one (1) year after the primary completion date
5.3.6.2. Delayed submission of results is permitted in certain circumstances.

5.4. Transferring a Record

5.4.1. If the Record Owner or PI is leaving the institution, it is their responsibility to inform the ORIO to ensure the record is appropriately monitored or transferred.

5.4.2. The Record Owner or PI can either be reassigned to another Record Owner or PI within the institution, or the record can be transferred to a new institution.

5.4.3. If the Responsible Party is moving a study from another institution, please contact the ORIO to help facilitate the record transfer.

6.0 References

6.1. 42 CFR 11;

6.2. NIH Policy on Clinical Trial Registration;

6.3. Food and Drug Modernization Act Section 50.3 (25)(e);

6.4. Food and Drug Modernization Act Section 113;

6.5. Food and Drug Administration Amendments Act (FDAAA) Section 801;

6.6. International Committee of Medical Journal Editors;

6.7. ORRP Guidance Clinical Trials Registration.