SECTION: RESEARCH
AREA: RESEARCH ADMINISTRATION
SUBJECT: REGISTRATION AND MAINTENANCE ON CLINICALTRIALS.GOV

PURPOSE

To establish the institutional requirements at the University of Arkansas for Medical Sciences ("UAMS") for registering and maintaining investigator-initiated Clinical Investigations with the ClinicalTrials.gov database.

SCOPE

This policy shall apply to all UAMS faculty, staff, and students conducting investigator-initiated human research studies covered under the provisions of US Public Law-110-85, Title VIII, Section 801 (Food and Drug Administration Amendments Act of 2007 or "FDAAA 801")[1], Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR 11)[2], National Institutes of Health (NIH) Policy on the Dissemination of NIH-Funded Clinical Trial Information[3], and Center for Medicaid & Medicare (CMS) Mandatory Reporting of an 8-Digit Clinical Trial Number on Claims, (CR 8401, TN 2955)[4].

This policy does not apply to industry-sponsored research or cooperative group ("co-op") or other studies where UAMS is not the lead site or Sponsor. These studies should be registered by the Sponsor or lead site in charge of the study.

DEFINITIONS

Clinical Investigation shall refer to the segment of clinical research for which an investigator directly interacts with participants in either an outpatient or inpatient setting[5], and shall include clinical trials, clinical studies, and registry studies that are qualified for coverage as specified in the Medicare National Coverage Determination ("NCD") Manual, Section 310.1[6], and in which claims for items and/or services associated with the Clinical Investigation could potentially be submitted to Medicare contractors.

Clinical Trial shall refer to a research study in which one or more human participants 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.[7]

ClinicalTrials.gov shall mean the registry and results database of publicly and privately supported Clinical Investigations conducted in the United States and around the world.

Device, as defined by Section 201(h) of the FD&C Act (21 USC 321(h)), shall mean an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is:

(1) recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them;
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or animals, or
(3) intended to affect the structure or any function of the body of humans or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of humans or animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Drug, as defined by Section 201(g) of the FD&C Act (21 USC 321(g)), shall mean:
(1) articles recognized by the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, official National Formulary or any supplement to any of them;
(2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals;
(3) articles (other than food) intended to affect the structure or any function of the body of humans or other animals;
(4) articles intended for use as a component of any article specified in the clauses above.

ICMJE shall mean International Committee of Medical Journal Editors.

IDE shall mean Investigational Device Exemption (also see Policy 16.1.11).

IND shall mean Investigational New Drug application (also see Policy 16.1.10).

Investigator shall mean an individual who actually conducts a Clinical Investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving a participant.

ORRA shall mean the Office of Research Regulatory Affairs, an organization that acts on behalf of UAMS to fulfill Sponsor responsibilities for Investigator-initiated studies conducted under UAMS-Sponsored INDs or IDEs, including preparation, filing and maintenance of IND or IDE applications, and study monitoring.

PI shall mean the Principal Investigator (lead Investigator) responsible for the conduct of a Clinical Investigation. The PI has access to and control over the data from the Clinical Investigation, has the right to publish the results of the Clinical Investigation, has the ability to meet all of the requirements for the submission of Clinical Investigation information and is ultimately responsible for complying with this policy and all related regulations.

PRS shall mean the ClinicalTrials.gov Protocol Registration and Results System, which is a web-based data entry system used to register a Clinical Investigation or submit results information for a registered study.

Record Owner shall mean the PRS account holder designated by the PI as responsible for registering a Clinical Investigation in ClinicalTrials.gov, maintaining and verifying the record, and

entering study results. The Record Owner in ClinicalTrials.gov will default to the PI unless another person has been designated by the PI.

Responsible Party shall mean the entity or individual who is responsible for performing quality verification of the study record and releasing it to ClinicalTrials.gov. The Responsible Party shall default to the Sponsor.

Sponsor shall mean an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization that takes responsibility for and initiates a Clinical Investigation. The Sponsor does not actually conduct the Clinical Investigation. The IND or IDE holder is considered to be the person or entity that initiated the Clinical Investigation and, therefore, is the Sponsor (regardless of how the Clinical Investigation is being funded).

POLICY

I. Required Registration:

The following Clinical Investigations must be registered in ClinicalTrials.gov:

1. **Applicable Clinical Trial:** An Applicable Device Clinical Trial or Applicable Drug Clinical Trial must be registered no later than 21 days after enrollment of the first participant. NOTE: Expanded access use is not considered an Applicable Clinical Trial.

    a. Applicable Drug Clinical Trial means a controlled Clinical Investigation of a health outcome using a drug or biological product subject to FDA regulations (i.e., FDA-regulated), other than phase 1 Clinical Investigations.

    b. Applicable Device Clinical Trial means a prospective Clinical Investigation of a health outcome involving a medical device subject to FDA regulation, other than a small feasibility or device prototype study (i.e., where the primary outcome measure relates to device feasibility and not to health outcomes). Pediatric post-market surveillance is also considered an Applicable Device Clinical Trial.

2. **NIH-Funded Clinical Trial:** All Clinical Trials funded in whole or in part by the NIH regardless of study phase, type of intervention, or whether they are subject to the statute and to the rule must be registered no later than 21 days after enrollment of the first participant.

    a. This does not apply to a Clinical Trial that uses NIH-supported infrastructure but does not receive NIH funds to support its conduct.

3. **CMS Qualifying Clinical Trial:** All Clinical Trials that are qualified for coverage as specified in the Medicare NCD Manual[6], and for which claims associated with the Clinical Trial could potentially be submitted to Medicare Contractors[4,6,8] must be registered and the 8-Digit Clinical Trial Number ("NCT number") provided before funding is released.

a. Clinical Trials funded by or supported by centers or co-ops funded by NIH, CDC, AHRQ, CMS, DOD and VA as well as Clinical Trials conducted under INDs or IDEs reviewed by FDA with potential Medicare claims are automatically CMS qualifying.

4. **UAMS-Sponsored IND or IDE:** A Clinical Investigation conducted by UAMS faculty, students, or staff under a UAMS-Sponsored IND or IDE.

   a. UAMS-Sponsored INDs or IDEs that are expanded access and multi-patient may be registered at the discretion of the PI and the Sponsor.

5. **Clinical Trial Intended for Publication:** To publish the results of a Clinical Trial, many journals, notably members of the ICMJE, require prospective registration of the study (i.e., prior to enrollment of the first subject) in a public database. The ICMJE requirements and a non-inclusive list of member publications are on the ICMJE website.[9] Therefore, it is suggested that any Clinical Trial that is intended to be published be registered in ClinicalTrials.gov.

II. Registering and Maintaining Registration of a Clinical Investigation:

1. It is the responsibility of the PI, or designee, to register all Clinical Investigations requiring ClinicalTrials.gov registration through the appropriate Sponsor.

   a. Investigator-initiated Clinical Investigations conducted by UAMS faculty, students, and staff shall register on PRS[10] under the "UArkansas" organization unless UAMS is not the Sponsor.

   b. Investigator-initiated Clinical Investigations conducted by UAMS faculty, students, and staff through Arkansas Children's Research Institute ("ACRI") that do not involve a UAMS-Sponsored IND or IDE shall be registered through ACRI.

   c. Industry-sponsored, co-op, or other Clinical Investigations where UAMS is not the lead site must be registered through the appropriate non-UAMS Sponsor.

2. The ORRA ClinicalTrials.gov Administrator(s)[11] shall create a UArkansas PRS account for the PI and any other study staff who may need access to the study record in PRS.

   To register the Clinical Trial, the Record Owner shall create a study record in PRS, enter all required and optional data elements, review to ensure the record is accurate and free of errors, and confirm the data entry is complete.

   The Responsible Party shall perform quality review of the record for accuracy, release it for PRS review, and assist the Record Owner address any errors, warnings, or notes identified by the PRS system or PRS Quality Control Review.

3. The Record Owner shall maintain the study record in PRS.

4. All Clinical Investigations entered into the ClinicalTrials.gov database are to be updated and verified by the Record Owner as soon as study information changes and as requested by either the PRS database or ORRA ClinicalTrials.gov Administrator(s).[12]

    a. Each record must be reviewed in its entirety and verified for accuracy at least every 12 months.

    b. Updates that must be made in ClinicalTrials.gov within 30 calendar days to include, but are not limited to, changes in the study start date, intervention name(s), overall recruitment status, individual site status, enrollment, primary completion date, study completion date, Responsible Party, expanded access availability, expanded access record, and protocol amendments.[13-14]

    c. Updates and corrections that must be made in ClinicalTrials.gov within 15 calendar days include, but are not limited to, changes in approval or clearance status of a Device product, PRS Quality Control corrections, and ORRA ClinicalTrials.gov Administrator or other Responsible Party quality verification corrections.

5. In the event that a PI intends to leave UAMS before all study results have been submitted to (and approved by) PRS, the PI (and/or Record Owner) shall alert the ORRA ClinicalTrials.gov Administrator(s) of the intended departure and plan moving forward.

    a. If UAMS is to remain the Sponsor of the study, the new PI will become the Record Owner in PRS.

    b. If the departing PI intends to continue and/or transfer the study, the ORRA ClinicalTrials.gov Administrator will facilitate transfer of the study record to the new Sponsor.

6. ORRA ClinicalTrials.gov Administrator(s) will notify the PI and/or the designated Record Owner regarding required maintenance of the study record. It is the responsibility of the PI to ensure the information is updated and/or corrected.

III. <u>Results:</u>

1. For all Applicable Clinical Trials and NIH-Funded Clinical Trials registered under the "UArkansas" Organization:

    a. Results for the Primary Outcome(s) must be submitted no later than <u>one (1) year</u> of the <u>Primary Completion Date</u>, which is "The 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 of the primary outcomes."[14]

b. If results information for Secondary Outcome(s) or additional adverse event information has not been collected by the Primary Completion Date, such information must be submitted no later than one (1) year of the Study Completion Date, which is "The 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."[14]

c. An IRB-approved protocol and statistical analysis plan (which may be a separate document or included in the protocol) must be submitted. An IRB-approved informed consent form that was used to consent a subject must also be submitted for any NIH-Funded Clinical Trial.

2. For all Clinical Investigations registered under the "UArkansas" Organization:

   a. Participant flow, demographic information, and baseline characteristic results must be submitted no later than one (1) year of the Primary Completion Date.

IV. **Non-Compliance:**

1. At the end of each month, the Vice Chancellor for Research and Innovation ("VCRI") will be notified of all registered Clinical Investigations that are out of compliance. The VCRI may choose to notify other institutional offices (e.g., Institutional Review Board ("IRB"), Office of Research Compliance ("ORC"), etc.) and/or choose to suspend or terminate the Clinical Investigation.

2. Failure to submit required registration and/or results information or submitting false or misleading information to ClinicalTrials.gov as well as failure to submit required certification or knowingly submitting a false certification of ClinicalTrials.gov registration in accordance with FDAAA 801[1] and 42 CFR 11[2] may lead to civil or criminal judicial actions, civil monetary penalties or grant funding actions.
   Grant funding actions for federally funded Clinical Investigations may result in loss of federal research funding by withholding remaining or future grant funds.

   Civil money penalties may be up to $10,000 (adjusted annually for inflation) for all violations adjudicated in a single proceeding and additional civil money penalties, up to $10,000 per day (adjusted annually for inflation), for each day not corrected within 30 days after the notice of noncompliance.

REFERENCES

[1] https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82

[2] https://www.ecfr.gov/cgi-bin/text-idx?node=pt42.1.11&rgn=div5

[3] https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm

[4] https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Downloads/Mandatory-Clinical-Trial-Identifier-Number.pdf

[5] https://www.ncbi.nlm.nih.gov/books/NBK222768/

[6] http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&bc=BAABAAAAAAAA&

[7] https://grants.nih.gov/policy/clinical-trials/CT-Definition-Case-Studies_1-4-18.pdf

[8] http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R310OTN.pdf

[9] http://www.icmje.org

[10] https://register.clinicaltrials.gov

[11] ORRAClinicalTrials-govadmin@uams.edu

[12] https://clinicaltrials.gov/ct2/manage-recs/faq#updatesToCT

[13] https://clinicaltrials.gov/ct2/about-studies/glossary

[14] https://register.clinicaltrials.gov/prs/html/definitions.html

Signature: _____ **Date:** **December 13, 2023**