Appalachian State University Research Protections and Institutional Review Board Standard Operating Procedures		
SOP #14	Clinical Trials	
Approved by IRB Chair	R. Andrew Shanely	Date: 04/22/2025
Approved by RP Director	Shante' Mathes	Date: 04/25/2025

I. PURPOSE

This document details Appalachian State University's IRB's standard operating procedures for research with human subjects that also meet the criteria as a *clinical trial*. Studies considered clinical trials must comply with varying requirements that do not apply to other types of human subjects' research. These requirements are designed to address the increased participant vulnerability and risks of many clinical trials compared with other research. The requirements that apply to clinical trials are described below. Appendices to this document provide resources for researchers and IRB staff regarding clinical trials requirements.

II. AUTHORITY

In accordance with 45 CFR 46, the HHS Policy for the Protection of Human Research Subjects, compliance with pertinent federal and State laws or applicable regulations that provide additional protections for human subjects must be followed. All non-exempt federally funded or contractually obligated human subjects' research studies that qualify as a *Clinical Trial* under 45 CFR 46.102(b) have additional obligations as defined in 45 CFR 46.116(h). Where applicable to FDA oversight, the FDA's requirements for clinical trials apply.

III. RESPONSIBILITY

1. Research personnel are responsible for complying with 45 CFR 46.102(b) and 45 CFR 46.116(h) for registering the study with and posting the clinical trial consent forms on the publicly available federal website clinicaltrials.gov. Refer to Appendices A and C.
2. Research protections (RP) staff are responsible for facilitating researcher access to clinicaltrials.gov and communicating researcher responsibilities to research personnel after IRB approval is granted. Refer to Appendix B.

IV. DEFINITIONS

1. Clinical Trial (HHS and NIH definition): Clinical trial means 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 the interventions on biomedical or behavioral health-related outcomes.
2. Clinical Investigation, FDA: An investigation or research that involves one or more human subjects, undertaken to assess/evaluate the safety or effectiveness of a test article (such as a drug or a medical device).
3. Health-Related Outcome, Behavioral: This is a change in a person's behavior that directly affects their health and wellness. This is often measured by behavioral assessments, psychological assessments, self-report, or observation. This can be a curriculum, a psychological method, a behavioral intervention, use of a wearable, etc.

4. Health-Related Outcome, Biomedical: This is an outcome directly related to the physical body. This can be measured through physical examination, lab testing, images, self-report, or observation. A biomedical outcome is directly related to the physical body and the changes the physical body undergoes because of the intervention being studied.
5. Intervention: includes both physical procedures by which information or biospecimens are gathered (*e.g.,* venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes (see 45 CFR 46.102(e)(2)).

V. PROCEDURES

A. Determining if a Study is Regulated as a Clinical Trial

The following criteria are used to determine whether a study is regulated as a *clinical trial*. All statements (1-6) below must be true for the study to be regulated as a *clinical trial* by Appalachian State University.

1. The study is subject to federal oversight because the research is:
    a. federally funded by a signatory of the Common Rule;
    b. affiliated with a sponsor/group that requires adherence to 45 CFR 46;
    c. subject to Food and Drug Administration (FDA) regulations; OR
    d. subject to the Department of Defense (DoD) regulations.
2. The study meets the regulatory definition of *research* under 45 CFR 46.102(l) and/or is regulated by the FDA:
    a. The study is a systematic investigation and designed to develop or contribute to generalizable knowledge, OR
    b. The study uses drug(s), biological product(s), medical device(s), or nutritional products (e.g., dietary supplements or foods) that are under the oversight of the Food and Drug Administration (FDA).
3. The study meets the regulatory definition for *human subject* under 45 CFR 46.102(e)(1):
    a. The study involves live humans (this also includes the secondary use of identifiable biospecimens); and
    b. The study uses or generates information about live humans.
4. The participants are *prospectively* assigned to one or more intervention groups:
    a. There is always a participant group that is exposed to the intervention(s) being researched.
    b. There may be a control group that does not get exposed to the intervention.
    c. There may be more groups beyond the two (control and intervention) groups, but this is not a requirement of qualifying as a clinical trial.
5. The study is designed to evaluate the effect of the intervention on participants' health:
    a. The research personnel are evaluating an intervention.
    b. An intervention is defined as a manipulation of the participant or participant's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
        i. Interventions are different from measurements. Measurements are used to collect data, while interventions are used to modify health-related endpoints. A manipulation or modification in one's behavior or environment for the purpose of measurement alone is not considered a clinical trial.
        ii. A manipulation or task is an intervention if it is used to modify a health-related biomedical or behavioral outcome. However, a manipulation or task used expressly for measurement, and not modification, would not be an intervention.

iii. Observational studies which do not include an intervention are not considered clinical trials.

c. The effect of the intervention evaluated is a health-related outcome. A health-related outcome is an outcome from the intervention being studied that directly influences a human as related to their physical health, psychological health, or behavior.
   i. A transient health-related outcome is sufficient for a study to be considered a clinical trial if all other elements of the clinical trial definition are met.
   ii. Studies eliciting opinions or preferences in the absence of an intervention are not considered to be clinical trials. However, studies that gather opinions from participants after an experimental manipulation or intervention, may be a clinical trial.
   iii. If the research personnel are comparing diagnostic performance of two approved diagnostic devices, this is not a clinical trial. A study must be designed to evaluate the effect of the intervention on the human participant to meet clinical trial definition.

B. IRB Approval Requirements for Studies Regulated as Clinical Trials

1. The IRB application must discuss the health-related outcomes that the study is examining.
2. The IRB application must discuss the best practices and standard of care as related to the study's intervention(s).
3. The proposed research must meet all of the criteria for approval as detailed in 45 CFR 46.111.
4. The consent/parental permission/minor assent must include information about the study as a clinical trial.

C. IRB Office Review and Processing of Federally Regulated Clinical Trials

1. The App State University IRB office will assess the study to ensure that all criteria are met for a clinical trials determination.
2. RP staff will register the principal investigator's App State email with clinicaltrials.gov so that when the study is approved by the IRB office, the researcher can register their study with clinicaltrials.gov.
3. When the study is approved, the IRB office staff will generate a clinical trials approval letter with information about researcher responsibilities regarding the clinical trial. This includes registration/login information to clinicaltrials.gov.

D. Registration and Reporting Requirements for Clinical Trials

1. Once IRB approval is received, the researcher must register the study on clinicaltrials.gov.
2. This must take place between when the study is approved by the IRB and no later than 60 days after the last study visit with the last participant. This includes:
   a. Registering the study on clinicaltrials.gov by completing their application and responding to all administrative feedback from the PRS administrators;
   b. Posting information about the study on the clinicaltrials.gov website; and
   c. Posting their final consent form after study is closed for recruitment, in accordance with 45 CFR 46.116(h)(3).
   d. Anything else required by Clinical Trials PRS or applicable regulations.

Appendix A
ClinicalTrials.gov Registration and Posting of Research Results

Registering a Study

Once you have received formal email notification that the IRB protocol corresponding to your regulated clinical trial was approved by the Appalachian State University IRB, you must register your study on clinicaltrials.gov website's PRS portal. Please see the approval letter uploaded with your IRB application for information about clinicaltrials.gov. If your clinical trial is subject to the FDA regulations, you have 21 days to complete this. If your study is not subject to the FDA regulations, the informed consent form must be posted after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol

You must have a PRS account to register a study. This should be issued with approval from AppalachianState University's IRB office. The Appalachian State IRB office, as a PRS affiliated organization, will initiate an account application for you (creating your login access). If you did not receive information about your PRS account, please email the Appalachian State IRB office to request a PRS log-in.

Once you have logged into the PRS portal, you will click on the "Records" button on the left hand, upper third of your screen. A menu of options will appear and you want to select "New Record." You will need to complete all sections of the application, upload requested documents, and submit the application to PRS. It's okay to copy and paste whatever you need from your eIRB application into the PRS portal, but the questions are sometimes very different from what Appalachian State asks. Furthermore, PRS' word allotment is far smaller than the word limit of the eIRB application's narrative response sections.

Registration must include the following information:

- **Description** (title, design, primary outcome measure information)
- **Recruitment** information (eligibility criteria, recruitment study, why study stopped if applicable)
- **Location and contact information** (name of sponsor, facility/PI/research team contact information)
- **Administrative data** (secondary ID, IRB protocol status)

The PRS Administrators will review your application for completeness. When the application passes review by the PRS Administrators, your study will be posted to the clinicaltrials.gov website.

Your application will be processed by the National Library of Medicine at the National Institutes of Health (NIH), typically within 48 business hours. They will also manage your ongoing access and interface within the PRS system. Because Appalachian State University and the Appalachian State University IRB office does not administer the PRS system, you will need to direct most questions about the PRS system to the PRS Administrators.

Posting Results

After your data collection is complete, you have 12 months to post your aggregated data to the PRS portal. You'll use the same log-in that you did to register the study. If you lost or cannot remember your PRS log-in, please email the PRS Administrators. Unfortunately, Appalachian State University and the Appalachian State University IRB office have no administrative privileges to reset your PRS log-in.

The following information is requested by the PRS portal for reporting research results: participant flow, baselines, and outcomes within the scope of the research; what, if any, adverse events occurred, limits and caveats of the research results, and who to contact for more information about the study. Complete all research results application sections and submit for review by the PRS Administrators. Once approved, the research study results will be posted to the clinicaltrials.gov website.

Be prepared to include the following in your PRS research results application:

- Progress of participants in each treatment group, including number who started and completed the trial
- Participant demographics and baseline characteristics (age, sex, gender, race, ethnicity, and all other measures assessed at baseline and are used in the analyses of the primary outcome measures
- Outcomes and statistical analyses for each primary and secondary outcome measure by treatment group or comparison group, include results of scientifically appropriate statistical analyses performed on these outcomes, if any
- Table of all anticipated and unanticipated serious adverse events and other adverse events that exceed a 5% frequency threshold within any group, including time event occurred, a description of the event, collection approach (systematic or non-systematic), and a table with the number and frequency of deaths due to any cause of treatment group or the comparison group
- Administrative information, included a point of contact to obtain more information about the posted summary results information

Appendix B
IRB Staff Checklist for Review

Answers to the 7 questions below must be "yes" to be considered a clinical trial at App State:

1. Is it research as defined by 45 CFR 46?
2. Is it human subjects research as defined by 45 CFR 46?
3. Is Appalachian State University engaged in the research?
4. Do the federal regulations apply for clinical trials?
    a. Is the study federally funded by a signatory of the IRB regulations?
    b. Is the study subject to the FDA or DoD regulations?
    c. If sponsored, is the study contractually obligated to follow the IRB regulations (the PI should have this information, but it may come later and the study amended)?
5. Are the participants prospectively assigned to one or more intervention group(s)?
6. Is the study designed to evaluate the effect of the intervention on the participants?
    a. The study must be specifically evaluating an intervention.
    b. This can be a manipulation of the subject or subject's environment
        i. Interventions are different from measurements. Measurements are used to collect data, while interventions are used to modify health-related endpoints. A manipulation or modification in one's behavior or environment for the purpose of measurement alone is not considered a clinical trial.
        ii. A manipulation or task is an intervention if it is used to modify a health-related biomedical or behavioral outcome. However, a manipulation or task used expressly for measurement, and not modification, would not be an intervention.
        Observational studies which do not include an intervention are not considered clinical trials
7. Is the effect being evaluated a health-related biomedical or behavioral outcome?
    a. Is the research being done on an intervention to evaluate a health-related outcome?
        i. There is an intervention in place that is being studied to assess the intervention's effect on health-related outcomes of any kind.
    b. A behavioral health outcome as related to assessing an intervention, is an outcome from the intervention that directly influences a human's behavior as related to their health and wellness. This is often measured by behavioral assessments, psychological assessments, self-report, or observation. This can be a curriculum, a psychological method, a behavioral intervention, use of a wearable, etc.
        i. For example, research on a curriculum implemented as an intervention that is intended to change the behavior of children's food intake and exercise.
        ii. For example, research on a therapy implemented as an intervention to change a person's behavior as related to their health and wellness.
    c. A biomedical health outcome as related to assessing an intervention, can be measured through physical examination, lab testing, images, self-report, or observation. A biomedical outcome is directly related to the physical body and

the changes the physical body undergoes as a result of the intervention being studied.

i. For example, a device or medicine intended to affect the body.
ii. For example, a movement or exercise intended to affect the body.

If the study is a clinical trial, the following must be completed by IRB staff:

- Note that the study is a clinical trial in the review notes for the study
- Set up the researcher's information in the PRS system for clinicaltrials.gov
- Generate the clinical trials approval letter for the study and send it to the researcher and upload it to the IRB application.
- The IRB Staff's involvement with the PRS system ends with facilitating the PI's access to it.

Appendix C

Researcher Responsibilities After Protocol is Approved by the Appalachian State University IRB Assigned Roles

1. Log into the PRS portal (which is the hub for clinicaltrials.gov) using the automated notice information provided to you post-IRB approval directly from PRS administrators via email. If you do not receive an email with the PRS portal information, please contact the Appalachian State IRB office at irb@appstate.edu.
2. Complete an extensive PRS portal application for your IRB-approved protocol. All questions about this process should be directed to the PRS administrators as the Appalachian State IRB doesn't administer clinicaltrials.gov. Your registration (or lack thereof) with clinicaltrials.gov will not invalidate your IRB approval, but it can affect your ability to publish your research results in journals and the Appalachian State IRB will make a finding of noncompliance.
3. Review and release the PRS protocol application to the PRS administrators to review. This is the responsibility of the investigator (PI) or, if the PI is a student, the faculty advisor for the clinical trial, not the Appalachian State IRB office.
4. Publicly post your consent form on a publicly available federal website that will establish a repository for clinical trial consent forms.
    a. The Appalachian State IRB office recommends using clinicaltrials.gov.
    b. The public posting will be done automatically by PRS administrators once they review and approve your PRS study application with its uploaded consent form. Note, IRB approval is a separate process from PRS approval.
    c. The Appalachian State IRB has no jurisdiction over when the PRS administrators review or approve your PRS application. Please plan accordingly.
    d. Posting your consent form is required by federal law (45 CFR 46.116(h)); failing to do so may result in a finding of noncompliance with the Appalachian State IRB office.
5. Post the consent form on clinicaltrials.gov after recruitment has closed and no later than 60 days after the last study visit by any subject, as outlined in the IRB-approved protocol.
6. Provide regular updates to the PRS portal regarding your study's progression and when the data collection is complete.
7. Publicly post the study's aggregated data on clinicaltrials.gov within 12 months of data collection completion. You do this by providing the information to the PRS portal, which will then post the information on clinicaltrials.gov.
8. Clinicaltrials.gov assigns the following roles:
    a. Appalachian State University is the "Sponsor Organization"
    b. The role of the Appalachian State IRB staff is "Administrator"
    c. The lead PI has multiple roles, including:
        i. "Responsible Party" - the individual responsible for verifying the accuracy of a study record and releasing it to ClinicalTrials.gov.
        ii. "Record Owner" – The PRS account holder who creates a study record in the PRS. Record owners can maintain the record themselves or give one or more users access to a record to make changes.