17.1 Executive Summary
This document addresses the policy and standard operating procedures for multisite or cooperative research with human subjects completed by NC State University researchers. In this document you will find the standard operating procedures for the use of Reliance Agreements and how the NC State IRB facilitates cooperative research.

17.2. Principle
North Carolina State University researchers engaging in federally funded research with human subjects that spans multiple sites or that is determined to be cooperative research as defined by 45 CFR 46.114 must have their research reviewed and approved by a single IRB before research with human subjects begins. Single IRB review and approval will be enacted for cooperative research and multisite studies through the use of Reliance Agreements.

17.3. Standard Operating Procedure (SOP)
A reliance agreement is an agreement between institutions allowing the IRB of one institution to rely on the IRB of another institution for review of human subjects research, by establishing the IRB-of-Record (which could be NC State or the other institution). The IRB-of-Record must hold a Federal Wide Assurance (FWA) with the Office of Human Research Protections (OHRP) of the U.S. Department of Health and Human Services (HHS). The Reliance Agreement must be signed by the Institutional Officials or designee at each institution. Based on the level of review or researcher affiliation, other types of agreements or acknowledgements may be required.

17.3.a. Types of Reliance Agreements
   1. Institutional authorization agreements (IAA) are agreements between two institutions with a current FWA.
   2. An IAA allows one institution with an FWA to rely on the IRB review of the other institution with an FWA.
   3. IAAs can cover one project or multiple projects as described in the agreement itself.
   4. IAAs are signed by the Institutional Official at each institution, or the Institutional Official's designee specifically empowered to sign such agreements.

ii. Individual Investigator Agreement
   1. An individual investigator agreement is an agreement between NC State University and a researcher who is not affiliated with an IRB that has an FWA.
   2. An individual investigator agreement binds the unaffiliated researcher to NC State University's rules and regulations regarding research with human subjects.
   3. An individual investigator agreement is signed by NC State University's Institutional Official (or the Institutional Official's designee) and the individual unaffiliated researcher.

iii. Letter of Acceptance of Exemption Determination
   1. If another institution's IRB has reviewed a study and given it an exemption determination, the NC State IRB can accept this determination for NC State investigators and not have to review the study independently. A Letter of Acceptance of
an Exemption determination is a letter that an IRB writes on behalf of their researcher that indicates that the IRB accepts the exemption determination of another IRB.

2. The NC State IRB will provide NC State researchers with this letter if the NC State researcher provides documentation that the reviewing IRB is aware that the NC State researcher is involved in the reviewed project and that all procedures that the NC State researcher will complete have been reviewed and approved by another IRB involved in the cooperative or multisite research.

17.3.b. Requesting a Reliance Agreement

i. In order for a Reliance Agreement to be enacted, a researcher must be “engaged in human subjects research.” If the researcher’s IRB makes such a determination, it may enter into a reliance agreement.
   1. An institution is determined to be engaged in research with human subjects when their employees or agents, acting on behalf of the institution, for purposes of a research project obtain (a) data about the subjects of the research through intervention or interaction with them; (b) identifiable private information about the subjects of the research; or (c) the informed consent of human subjects for the research.
   2. Employees or agents refers to individuals who:
      a. act on behalf of the institution;
      b. exercise institutional authority or responsibility; or
      c. perform institutionally designated activities.

   “Employees and agent” can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

ii. An Institutional Authorization Agreement can be reviewed and approved concurrently to the review of the research project. This means that the IAA can be submitted to the IRB at initial submission of the research protocol, during review of the protocol, or after the protocol has been approved. The agreement cannot be executed until the research study has been approved.
   1. The IRB application and approved protocol must clearly state that the study involves cooperative or multisite research plans and the collaborators involved in the project must be named and their role detailed in the IRB application/protocol. This can be completed during initial review or as an amendment to an approved protocol.
   2. Once the Institutional Authorization Agreement is signed by the Institutional Officials (or designees) from the other institution with an FWA and NC State University, and the study is approved an IRB, the researchers from the relying institution can begin work on the IRB-approved research project.

iii. Site Context Review (also called local context review) is a type of review that relying IRBs provide to reviewing IRBs. This information provides the reviewing IRB with all the necessary information needed to make final decisions regarding human subjects’ protections and compliance at individual sites. The details of the site context review requirements are noted below:
   1. When NC State is serving as the IRB of record all relying IRBs must provide NC State University with the necessary information to complete a robust review to assess the risks/benefits to participants and other issues of compliance.
a. Applicable Laws: Relying IRBs must provide NC State with any applicable information relating to local and state laws that may apply to the research.

b. Conflict of Interest Information – Relying IRBs must provide NC State University with all relevant “Conflict of Interest” information that is pertinent to the research being reviewed. This includes up to date disclosures and any real or perceived conflicts of interest related to the proposed research project. Please also see NC State’s IRB’s COI policy.

c. Ancillary Reviews – these are reviews that are required for other aspects of the study in order for the study to take place. These can be reviews such as
   i. Institutional Biosafety Committee (IBC), Radiation Safety, Institutional Animal Care and Use Committee (IACUC), HIPAA, Data Security, Export Control, other applicable reviews
   ii. Organization/University applicable Rules and Regulations
   iii. Organization/University IRB applicable Policies and SOPs

d. Proof of completion of Research with Human Subjects training. All researchers involved in the proposed project must provide proof of current training for research with human subjects. This training content should be applicable to the proposed research and the risks specific to the proposed research.

2. When NC State is the Relying IRB
a. Applicable Laws: NC State University’s IRB will provide the reviewing IRB with any applicable information relating to local and state laws in North Carolina that may apply to the research.

b. Conflict of Interest Information – NC State University’s IRB will provide the reviewing IRB with all relevant “Conflict of Interest” information that is pertinent to the research being reviewed. This includes up to date disclosures and any real or perceived conflicts of interest related to the proposed research project.

c. Ancillary Reviews – these are reviews that are conducted as appropriate for the project and are likely required for other aspects of the study that may be required in order for the study to take place. These can be reviews such as
   i. IBC, Radiation Safety, IACUC, Export Control
   ii. NC State University applicable Regulations
   iii. NC State IRB applicable Policies and SOPs

d. Proof of completion of Research with Human Subjects training. All researchers involved in the proposed project must provide proof of current training for research with human subjects. This training content should be applicable to the proposed research and the risks specific to the proposed research.

e. NC State will comply with all other reasonable requests put forth by the reviewing IRB. NC State will provide necessary information to the reviewing IRB in a timely manner.

iv. An Individual Investigator Agreement is a formal agreement between NC State University and an individual researcher who is not affiliated with an IRB. This agreement can be reviewed and approved concurrently to the review of the research project. This means that the individual investigator agreement can be submitted to the IRB at initial submission of the research protocol, during review of the protocol, or after the protocol has been approved. The agreement cannot be executed until the research study has been approved.
1. The IRB application and approved protocol must clearly state that an unaffiliated investigator is involved in the project and detail the unaffiliated investigator’s role.
2. Once the Individual Investigator Agreement is signed by the individual and NC State University’s Institutional Official (or designee) and the study is approved by the NC State IRB, the individual investigator can begin work on the research project following the approved procedures.

17.3.c. Record Retention and Communication Between IRBs

i. When NC State is the Reviewing Institution (IRB of Record)
   a. Records must be retained and maintained for a minimum of three years and a maximum amount of time as required by the study procedures and applicable retention rules.
   b. Communication expectations for issues such as reportable events, renewals, amendments, personnel updates, consent posting requirements, expectations for post approval monitoring, and how participant complaints are to be addressed must be included within the IRB application as procedures to be approved.

ii. When NC State is the Relying Institution
   a. Records must be retained and maintained for a minimum of three years and a maximum amount of time as required by the study procedures.
   b. Communication expectations for issues such as reportable events, renewals, amendments, personnel updates, consent posting requirements, expectations for post approval monitoring, and how participant complaints are to be addressed will be included as the reviewing institution requires.

17.3.d. Single IRB Review and Approval

Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

i. Cooperative Research (45 CFR 46.114)
   1. Applies to all research located in the United States that is engaged in research that involves more than one institution.
   2. Exception: Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

ii. National Institute of Health (NIH) Multi-Site Studies
   1. The use of a single IRB (sIRB) is required by NIH for all domestic sites of NIH funded studies where each site will conduct the same protocol involving non-exempt human subjects’ research, whether supported by grants, cooperative agreements contracts, or the NIH Intramural Research Program.
   2. Plans for the use of an sIRB must be included in all grant applications and contract proposals that are submitted to NIH.
   3. This does not apply to foreign sites, career development, institutional training or fellowship awards. The policy allows for exceptions in the following instances:
a. Sites for which federal, state, or tribal laws, regulations or policies require local IRB review.
b. Other exceptions to allow for local IRB review may be considered by NIH based on compelling justification. These other exceptions must be reviewed and approved by NIH. Please see NOT-OD-18-003 for more information about exceptions to the policy.
c. The NIH sIRB policy allows the consideration of requests for other exceptions not based on a legal, regulatory, or policy requirement, if there is a compelling justification for the exception. These other exceptions must be reviewed and approved by NIH.
Appendix A
Definitions

Multi-Site Study: A multi-site study that uses the same protocol to conduct non-exempt human research at more than one site.

Participating Site: In a multi-site study a participating site is a domestic entity that will rely on the sIRB to carry out the site's IRB review of human research for the study. In eIRB+ this is called a "pSite", in which a separate submission will be required for each external site relying upon the NU IRB.

sIRB: An sIRB (Single Institutional Review Board) is the selected IRB of record that conducts the ethical review for participating sites of a Multi-Site Study.

Relying IRB: An IRB designating via an agreement to cede review to an external IRB for a particular study.

Cooperative Research: research that involves more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. The Institutional Official (IO) is the individual who is legally authorized to act for each institution and, on behalf of the the institution, obligates the institution to the terms of its Federalwide Assurance.

Independent IRB is a review board that is not owned or operated by the research organization for which it provides review services. It is not associated with an institution. An Independent IRB is subject to the same federal and state regulatory requirements applicable to all IRBs. Some research institutions have contracted with Independent IRBs to provide outside review. Some institutional IRBs delegate jurisdiction and accept the review of an independent IRB when their institution is participating in a Multi-Site Study.

- Independent Federal IRB is an Independent IRB created by a federal agency to support multiple institutions, generally for specific types of research
- Independent Commercial IRB is a for-profit Independent IRB that provides services for academic and non-academic institutions and researchers for a fee. They are hired to review research.

Single IRB is the IRB of record, selected on a study-by-study basis, which provides the ethical review for all sites participating in a Multi-Site Study. A Single IRB may be either an Independent IRB or associated with an institution engaged in the Multi-Site Study.

Central IRB is the IRB of record that provides the ethical review for all sites participating in a Multi-Site Study. Generally, “Single IRB review” and “Central IRB review” mean the same thing: a Single IRB of Record overseeing all sites participating in a Multi-Site Study.

IRB Of Record: The IRB of Record assumes primary responsibility for the review and approval of a study. Any IRB overseeing human subject protections for a study is considered the IRB of Record.

Federal Wide Assurance (FWA): A Federal Wide Assurance (FWA) is the documentation of an institution’s commitment to comply with federal regulations and maintain policies and procedures for the protection of human participants. An institution must have an FWA in order to receive Department of Health & Human Services (DHHS) support for research involving human subjects. This is the principal mechanism for compliance oversight by the Office for Human Research Protections.