1. PURPOSE

This procedure describes the process to establish a Reliance Agreement with another IRB. A Reliance Agreement (also called an Institutional Authorization Agreement, or IAA) is a document signed by two or more institutions engaged in human subjects research that permit one or more institution(s) to cede review to another IRB. Both the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) permit an IRB the option to rely on the review of another IRB. Avera IRB retains authority to determine whether to conduct its own IRB review on a project-specific basis, particularly for industry-funded and investigator initiated studies.

Effective January 25, 2018, National Institutes of Health (NIH) mandated the use of single IRBs (sIRB) as a contingency for funding of multi-center studies. See section 5.2 below for details of the sIRB Policy for Multi-Site Research with the NIH.

Effective January 20, 2020, the Cooperative Research provision of the Common Rule mandated sIRB oversight for virtually all federally funded multisite research. See section 5.1 below for details on the sIRB requirement in the Common Rule.

Avera 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 sIRB before research with human subjects begins.

2. DEFINITIONS

- **IRB:** An Institutional Review Board is a committee charged with providing regulatory oversight for research involving human subjects.
- **sIRB**: A single IRB, also termed “central” IRB. An IRB that provides IRB review and oversight for two or more participating sites in multi-site research. The IRB may be associated with an academic, private, non-profit, or commercial entity.
- **External IRB**: The reviewing IRB for a study occurring at Avera, that is not part of Avera IRB, but rather another institutional IRB or a commercial IRB.
- **Reliance Agreement:** A written agreement between entities participating in multi-site research. The Reliance Agreement contains terms that describe what each entity is responsible for in the review, oversight, and conduct of the research. These are also referred to as IRB Authorization Agreements, and IAAs.
- **Relying Institution:** A term used in Reliance Agreements to identify the party to the agreement that will rely on an IRB outside of its own entity. These are also referred to as the Relying Institution, Relying Site or Participating Site.
- **Reviewing IRB:** A term used in Reliance Agreements to identify the party to the agreement that acts as the sIRB in providing IRB review for all sites participating in the conduct of the same multi-site protocol.

3. PROCEDURE

Avera IRB retains authority to determine whether to conduct its own IRB review on a project specific basis, particularly for industry-funded and investigator initiated studies. The Avera Human Research

Protection Program (HRPP) ensures the safe and ethical conduct of all human subject research conducted at Avera, and retains oversight of human subjects research conducted by Avera physicians, staff and students. As part of the Avera HRPP, the Avera IRB provides IRB review and oversight under the Avera HRPP unless an alternate IRB has been approved through a formal written Reliance Agreement between Avera and the alternate IRB.

IRB oversight for multi-site research studies may be provided via a sIRB model or with each site providing its own local IRB oversight. All research that is funded by NIH and falls under the NIH sIRB Policy must use a sIRB for the research conducted in the US as designated in the funding application. All research that falls under the DHHS regulations related to Cooperative Research (45 CFR 46.114) must use a sIRB for the research that is conducted in the US. This includes other agencies that have signed onto the Common Rule.

All protocols for research performed at Avera must be provided to the Avera IRB, whether or not the Avera IRB is acting as the sIRB for the research. When researchers rely on an external IRB, Avera HRPP will generally exempt researchers from duplicative reporting. However, reports of Unanticipated Problems (UPs) and Major Protocol Deviations must be made to both the Avera IRB and the reviewing IRB. If the study is not overseen by the Avera IRB, a copy of the submission that was made to the reviewing IRB may be forwarded and emailed to the Avera IRB.

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 Avera 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.

For multi-site studies not falling under the criteria of the NIH Single IRB policy or the single IRB Common Rule requirement, such as industry-sponsored, foundation-sponsored, or unsponsored studies, single IRB review is not required by the regulations.

4. SPECIFIC PROCEDURES

4.1 For Industry-Funded Research - Types of Reliance Agreements

A. Institutional Authorization Agreement (IAA)

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.

B. Master Reliance Agreement

1. A Master Reliance Agreement is utilized when multiple studies cede review to a specific external IRB. Master Reliance Agreements may be reciprocal in that signatory institutions can act as the site providing IRB review and oversight or the site relying. Master Reliance Agreements may be for a single protocol or a number of protocols that are negotiated on a case by case basis.

C. Letter of Acceptance of Exemption Determination

1. If another institution's IRB has reviewed a study and given it an exemption determination, the Avera IRB can accept this determination for Avera 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.

4.2 Requesting to Use a Central IRB

In general, Avera IRB will have "right of first refusal" for oversight of all research happening at an Avera facility. The process to request that a study be allowed to go to a central IRB is as follows:

A. Email the IRB Manager, or Executive Director of Research Compliance, the completed "Form to Request Central IRB". Include in this request a copy of the protocol, consents with local Avera language inserted (including the pregnancy-prevention language and other edits, if applicable, and any other relevant study documentation.

1. The IRB will conduct an administrative review of the external IRB request.
    a. Part of the review process will be to have a subject expert review the proposed research to ensure the Ethical and Religious Directives (ERDs) are adhered to, and that the proposed research does not go against these directives.
2. If the IRB determines that this is not acceptable, for any reason, the IRB will email this decision back to the study team and inform them that the study will need to go to the Avera IRB.
3. If the IRB finds the use of the external IRB to be acceptable, they will informally agree to this by email, so that the process may continue forward.
    a. If approved to proceed with an external IRB, and a Master Reliance Agreement <u>is</u> already in place, then the IRB Manager will inform the regulatory team that the study may proceed, and will provide a letter to the Central IRB, to include when submitting to that IRB.
    b. If approved to proceed with an external IRB, and a Master Reliance Agreement <u>is</u> <u>not</u> already in place, then the regulatory team that is preparing the study for the external IRB submission should complete the external IRB's Reliance Agreement for the specific study and email that to the IRB.
        1. The IRB Manager will send the IAA to the IO for signature, and will return the partially executed (PE) IAA to the regulatory team once it's signed.
        2. The regulatory team will be responsible to ensure Avera required wording in informed consents are in

alignment with the Ethical and Religious Directives (ERDs) that Avera adhere to.

B. After the regulatory team gets the research study approved with the Central IRB and has a fully executed IAA (if a Master Reliance Agreement is not already in place), a copy should be forwarded to the IRB Manager.

4.3 Event Reporting Responsibility

Although Avera HRPP will generally exempt researchers from duplicative reporting, reports of Unanticipated Problems (UPs) and Major Protocol Deviations must be made to both the reviewing IRB and the Avera IRB. To simplify this process a copy of the submission that was made to the reviewing IRB may be forwarded by email to the Avera IRB.

5. Single IRB (sIRB) Review and Approval

Any institution located in the United States that is engaged in cooperative research must rely upon approval by a sIRB for that portion of the research that is conducted in the U.S. 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.

5.1. Federally Funded Cooperative Research (45 CFR 46.114)

A. Cooperative Research projects are those projects covered by the 2018 Common Rule that involves more than one institution.

B. The sIRB compliance date for cooperative research went into effect on January 20, 2020, and requires sIRB review for virtually all federally funded cooperative research projects located in the U.S.

C. Exception: Cooperative research for which more than sIRB 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.

5.2. National Institute of Health (NIH) Multi-Site Studies

A. NIH expects that all domestic sites participating in multi-site studies, which involve *non-exempt human subjects research funded by the NIH*, will use a sIRB to conduct the ethical review required for the protection of human subjects, whether supported by grants, cooperative agreements contracts, or the NIH Intramural Research Program.

B. Plans for the use of a sIRB must be included in all grant applications and contract proposals that are submitted to NIH.

C. National Institutes of Health (NIH) mandated the use of sIRBs as a contingency for funding of multi-center studies effective January 25, 2018.

D. This does not apply to foreign sites, career development, institutional training or fellowship awards. The policy allows for exceptions in the following instances:

1. Sites for which federal, state, or tribal laws, regulations or policies require local IRB review.
2. 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.

3. 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.

D. Each participating site will need to establish a reliance agreement, also known as IAA, with the sIRB. The Avera IRB has already signed onto the SMART IRB agreement. The SMART IRB agreement eliminates the need to establish a study-specific agreement and may be an option for many of the NIH funded studies.

6. Site Context Review

Site Context Review is primarily used for studies under the Common Rule, such as the sIRB for NIH funded studies and Cooperative Research. 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.

6.1. For all types of studies when Avera is the Relying IRB

A. Applicable Laws: Avera's IRB and/or HRPP will provide the reviewing IRB with any applicable information relating to local and state laws in South Dakota that may apply to the research.

B. Conflict of Interest Information – Avera IRB and/or HRPP 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:

a. IBC, Radiation Safety, IACUC, Export Control
b. Avera IRB applicable Policies and SOPs

D. Proof of completion of Research with Human Subjects training, (CITI 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. Avera IRB will comply with all other reasonable requests put forth by the reviewing IRB, and will provide necessary information to the reviewing IRB in a timely manner.

6.2 Avera as the IRB of record

A. The Avera IRB will not, at this time, serve as the sIRB/IRB of record for multi-site studies and other institutions/sites engaged in human research.

7. IRB Records

The Avera IRB will maintain a list of all studies at Avera that are being reviewed by an external IRB.

8. RESPONSIBILITY

The IRB Manager or Executive Director of Research Compliance will determine if a Reliance Agreement will be allowed, on a study-by-study basis.

The regulatory contact will prepare the Reliance Agreement, and email it to IRB Manager for IO signature.

The regulatory contact will be responsible to ensure Avera required wording in informed consents are in alignment with the Ethical and Religious Directives (ERDs) that Avera adhere to.

9. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.114

NIH single IRB Policy:

https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm

21 CFR 56.114

REVISION HISTORY

Revision Number	Version Date	Approved By	Date Approved
2.0	1/21/2021	Avera Institutional Official	2/12/2021
• When requesting to use an external IRB, the ICs should first be edited to have all Avera appropriate language inserted, prior to sending to the IRB for review (along with the protocol, etc.) • Other minor administrative edits.			
1.0	7/14/2020	Avera Institutional Official	9/16/2020
• New Procedure			