

SOP - Multi-Site Research and IRB Reliance Process

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Institutional Review Board

University of Missouri-Columbia

Standard Operating Procedure

Multi-Site Research & IRB Reliance Process

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Associate Vice Chancellor for Research

A handwritten signature in cursive script that reads "Michele Kennett".

1.0 Purpose

This policy applies to all multi-site human subject research, regardless of funding source. The policy outlines the IRB review process for multi-site research and the use of a single IRB (sIRB).

2.0 Scope

Non-exempt multi-site research activities are subject to special procedures for coordination of research review and may involve more than one IRB responsible for research oversight. In these cases, MU established additional procedures to define the responsibilities of each HRPP/IRB, coordinate communication among responsible IRB committees, and manage information obtained in multi-site research to ensure protection of human subjects. In coordinating these reviews, the MU HRPP/IRB staff, in consultation with the Institutional Official and Legal Counsel, if needed, take into consideration the source of funding for the research activity, federal regulations, specific sponsor regulations governing human research protections, and institutional policy. The Associate Vice Chancellor of Research serves as the Signatory/Institutional Official for MU.

MU may enter into formal agreements with other sites which are not legal entities of MU to provide IRB review (i.e., to act as the reviewing IRB), to rely on other institutions for IRB review, or to cooperate in the IRB review process. MU enters into these types of arrangements through a memorandum of understanding, IRB authorization/reliance agreement, or contract with the institution(s).

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MU is a participating institution in the SMART IRB online platform where investigators and institutions can request, track, and document reliance/authorization agreements. The SMART IRB Master Common Reciprocal Institutional Review Board Authorization Agreement clearly defines roles and responsibilities. SMART IRB is often used with MU multi-site research and is documented in eCompliance for each project utilizing this agreement. Investigators can use the online platform to document reliance or an acknowledgement template the MU IRB can fill out and share with the other site(s).

Exempt multi-site research activities are discussed at the end of this policy.

AAHRPP Accreditation

As of January 21, 2020, MU will only rely on an external IRB that is AAHRPP accredited, or on an IRB that MU IRB determines has appropriate human subject protections given the potential risks to participants. If MU IRB is relying on a non-AAHRPP accredited IRB, the MU HRPP/IRB office will conduct an administrative review of the reliance submission to ensure compliance with MU's ethical standards and with applicable laws and regulations. The extent of the review can vary, depending upon the level of risk to participants in the research.

AAHRPP outlines in Standard I-9 requirements to ensure that, when sharing oversight of research with another organization, the rights and welfare of research participants will be protected. The authorization/reliance agreement outlines the responsibilities and requirements under this standard.

Federally Supported Cooperative Research:

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. The following research is not subject to this provision:

- i. Cooperative research for which more than single IRB is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe);
or
- ii. 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.

This requirement goes into effect January 19, 2020, except funding through the National Institutes of Health discussed below.

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National Institutes of Health (NIH):

As of January 25, 2018, NIH expects that all sites participating in multi-site studies, which involve non-exempt human subjects research funded by the NIH, even if not covered by US regulations, will use a single IRB to conduct the ethical review required for the protection of human subjects.

1. Authorization agreements, also called reliance agreements, document respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.
 - a. The requirement for a single IRB review applies to awardees in the US and participating research sites in the US.
 - b. The requirement for single IRB review does not apply to organizations outside the US.
 - i. MU IRB will not serve as the Single IRB for international sites.
 - c. The awardee organizations are responsible for ensuring authorization agreements are in place, and that documentation is maintained.
 - d. It will be documented who is responsible for meeting additional certification requirements, such as Certificates of Confidentiality or the NIH Genomic Data Sharing Policy.
 - e. Participating sites are expected to rely on the single IRB, though they may conduct their own review in accordance with NIH policy on exceptions from single IRB review.

Additional information can be found on the NIH website:

<https://grants.nih.gov/policy/clinical-trials/single-irb-policy-multi-site-research.htm>

3.0 Policy/Procedure

Determining the IRB of Record

1. For multi-site research, it is determined whether each site is “engaged” in research according to the guidance outlined in the Office for Human Research Protections (OHRP) Engagement Guidance by considering the nature of the involvement of site personnel in implementing research procedures and/or collecting data at the site.
 - a. If the site is engaged in research, it is determined whether the site requires a Federalwide Assurance if they do not already have one.
 - b. If the site engaged in research has its own IRB responsible for conducting the IRB review for that site, they may choose to review its own participation in the research or enter into a reliance agreement with the MU IRB.
 - c. In cases in which research undergoes joint IRB review at MU IRB and at the non-MU site, an IRB authorization agreement is not necessary. Staff evaluates each situation on a case-by-case basis.
 - d. In many cases, however, the site may enter into an agreement allowing the site to rely on the MU IRB to review, approve, and provide continuing oversight of the multi-site research. As noted above, federally funded studies must enter into an authorization agreement and rely upon a sIRB.
2. The IRB Reliance Liaison in conjunction with the Institutional Official and MU Legal Counsel, if necessary, makes the final determination whether the MU IRB will serve as the reviewing or relying IRB.

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3. MU IRB may agree to defer responsibility for IRB review to an external IRB. To defer responsibility, the external IRB must have an approved IRB registered with the Office of Human Research Protections.

Examples of circumstances in which MU may defer IRB review may include cases where:

- a. the funding agency requires it;
 - b. the MU employee role is limited, such as data analysis only;
 - c. the research began at another institution prior to employment of the investigator at MU and remains active only at the other institution (and any funds supporting the research remain under the control of the non-MU institution), or
 - d. other studies as appropriate.
4. When the MU IRB conducts IRB reviews for other sites, the IRB ensures sufficient knowledge of local research context for the location as detailed in the section on *IRB Knowledge of the Local Research Context*.

MU is the Lead Site – External Sites not Relying on MU IRB

1. If MU is the lead site in a multi-site study or the MU investigator is the lead investigator, the PI provides additional information to the MU IRB to ensure ongoing communication among the participating IRBs and sites.
2. Additionally, the MU investigator must submit to the IRB a written plan for the management of information that is relevant to the protection of human subjects, such as reporting unanticipated problems, protocol modifications, and interim results from all participating sites.

MU IRB is the IRB of Record

1. MU investigators should submit the Initial Request for MU to be the IRB of Record for multi-site research. The request may also be made within the IRB application, but the investigators risk the chance of the MU IRB not agreeing to serve as the IRB of Record and may cause delays in the IRB approval process.
2. The MU IRB will determine whether it can serve as the IRB of Record taking into consideration IRB expertise, number of external sites, and resources necessary to serve in this capacity.
3. Notification will be sent to the MU investigators along with the estimated IRB fees associated with performing the IRB reviews. The Authorization Agreements can start to be negotiated at this time and must be executed prior to IRB approval of the external site(s).

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4. MU investigators will be directed to seek IRB approval for the MU site first including model documents (i.e. consent, recruitment) for external sites, then after initial approval, submit the Amendment for External Sites to obtain approval for the external, relying site(s). The local context form for each external site must be uploaded at this time along with their site-specific documents seeking IRB approval.
 - a. The Amendment for External Sites must only be used to seek approval of external site-specific documents. The main Amendment Form must be submitted to seek approval for overall study documents utilized by all external sites (i.e. protocol changes).
5. MU investigators will serve as the coordinating site and are responsible for submitting any study wide post-approval reportable items by following applicable MU IRB policies.

MU IRB Serving as the IRB of Record for an External Site without their own IRB

1. MU may enter into a formal agreement to serve as the relied-upon IRB for a single site, which is not a legal entity of MU, by signing a memorandum of understanding, contract, or other official written agreement. Unlike the IRB Authorization Agreement, which applies to single projects, a formal agreement provides for ongoing IRB oversight of some or all of the research involving human subjects at the external site.
2. In these cases, the formal agreement outlines the relationship between the institutions and documents the authority granted to the institution to serve as the relied-upon IRB for the site.
3. Sites operating under a formal agreement must file their own individual assurance with the OHRP and list the appropriate MU IRB committee(s) as the designated IRB on the assurance. The Signatory Official for each institution signs all formal agreements.
4. The terms of the formal agreement specify appropriate human subjects education and training resources for investigators at the cooperating site as well as education and training for MU IRB members pertaining to IRB knowledge of the local research context. See the section on *IRB Knowledge of Local Research Context* for additional details.
5. The MU Division of Research, Innovation, and Impact and MU IRB Office maintains a record of current formal agreements onfile.

Negotiating an IRB Authorization Agreement

1. Research studies involving multiple engaged institutions may rely on a single IRB. In such cases, participating IRBs enter into a written agreement identifying the specific IRB designated to provide review and detailing the respective responsibilities of the IRB and each institution under the agreement.
2. Under an IRB Authorization Agreement, both institutions agree that one institution is responsible for providing IRB review and the second will rely on the other for IRB review for a single specified project. IRB Authorization Agreements list the federal assurance

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number for each institution, if applicable, designate the specific project to which the agreement pertains, and specify that the agreement applies to no other research projects.

3. The Authorized Officials for both institutions must approve the agreement in writing. The Institutional Official signs all IRB Authorization Agreements for MU under its assurance. Both institutions maintain an IRB Authorization Agreement on file and agree to submit the document to OHRP upon request.
4. The reviewing IRB has the responsibility for initial and continuing review of the research. The reviewing IRB takes into account the required criteria for approval, the applicable regulations (e.g. 45 CFR 46, 21 CFR 50 or 56), the facilities and capabilities of the other institution, the measures to be taken by the participating institution to ensure compliance with the IRB's determinations, and community attitudes or local research context, as appropriate. (See the section on *IRB Knowledge of Local Research Context* for additional information.)
5. The reviewing IRB under an IRB Authorization Agreement is responsible for conveying approvals to all participating sites, either directly to the IRB or through the respective PI.
6. In cases in which MU relies on another IRB under an IRB Authorization Agreement, the PI, with assistance from the IRB, is responsible for providing information to the non-MU IRB assuring sufficient consideration of local research context for the MU component(s) of the study.
7. When the MU IRB relies on another IRB for review of research under an IRB Authorization Agreement, it agrees to abide by the decisions and determinations made by the non-MU IRB.
8. Likewise, individual investigators agree to abide by those same decisions and determinations and may not modify or alter the research protocol without prior written approval of the non-MU IRB.
9. The PI sends all required reports directly to the non-MU IRB with copies to the MU IRB, as appropriate according to the authorization agreement.
10. Additional information on the negotiation of sub award agreements for multi-site sponsored research is found in the Office of Sponsored Projects Administration/IRB Coordination SOP.

IRB Knowledge of Local Research Context

1. In accordance with OHRP guidance, when the MU IRB serves as the relied-upon IRB for another institution or when the research involves distinct subject populations (non-English speaking populations, veterans, etc.), the MU IRB ensures that it possesses or obtains sufficient knowledge of the local research context even when the IRB is geographically removed from the research location.
2. The PI supports the IRB in understanding the local research context by providing the IRB necessary information, as appropriate, on:
 - The anticipated scope of the site facility's research activities;
 - The types of subject populations likely to be involved;
 - The size and complexity of the institution;
 - Institutional commitments and regulations;
 - Applicable law;
 - Standards of professional conduct and practice;
 - Method for equitable selection of subjects;
 - Method for protection of privacy of subjects;

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- Method for maintenance of confidentiality of data;
 - Languages understood by prospective subjects;
 - Method for minimizing the possibility of coercion or undue influence in seeking consent;
 - Safeguards to protect the rights and welfare of vulnerable subjects.
3. In cases where the MU IRB conducts non-local review, members must have sufficient knowledge of the community from which the subjects are drawn to ensure protection of subject rights and appropriateness of the consent process for the subject population. In addition, the IRB must be sensitive to community laws and mores. The IRB may ensure the necessary expertise and knowledge to make appropriate determinations regarding the local research context through one or more of the following activities, as appropriate to the level of risk and in accordance with OHRP guidance and FDA regulation:
 - Personal knowledge of the local research context on the part of one or more IRB members, such knowledge obtained through extended direct experience with the research institution, its subject populations, and its surrounding community;
 - Review of the proposed research by representatives from the facility or by one or more ad hoc or cultural consultants with knowledge of the local research context. Ad hoc or cultural consultants may provide comments or recommendations in writing to the IRB prior to the meeting or attend the convened meeting to participate in the review, either physically or through audiovisual or telephone conference, when participation is deemed warranted by the consultant(s) or any one member of the IRB;
 - Systematic reciprocal documented interchange between the IRB and elements of the local research context through periodic visits to the research site by one or more IRB members/IRB staff or University representatives in order to obtain and maintain knowledge of the local research context; periodic discussion with appropriate consultants knowledgeable about the local research context; interaction with one or more designated institutional liaisons; and/or review of relevant written materials;
 - Appointment of an IRB member from the community in question.
 4. IRB staff assists the PI in addressing the requirements for information on the local research context upon request.
 5. IRB staff assists the IRB in identifying appropriate consultants and distributing appropriate review materials pertaining to the local research context to IRB members, as appropriate.
 6. IRB staff maintains documentation in the database and the study file of the local research context and the measures taken to ensure sufficient IRB knowledge of that context.
 7. The IRB may include the name and contact information for an IRB contact in the consent document for non-local IRB review or designates an individual at the research site to serve as the contact to relay reports to the IRB.
 8. In the minutes of the meeting or in the IRB file, IRB staff or the IRB reviewer documents the procedures used to ensure that the IRB adequately considered community attitudes.

MU Investigator Responsibilities When MU IRB is Relying on an External IRB

1. The initial request to rely on another IRB is a two-step process in eCompliance. The MU investigator must submit an Initial Reliance Request Form in eCompliance to request to rely on an external IRB. At minimum, the investigator should include:
 - a. Protocol

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- b. Model Consent
 - c. PI's name
 - d. Sponsor Name
 - e. Proposed IRB of record.
2. When the investigator receives initial approval from the MU IRB, they are to work with their sponsor and/or IRB of Record to secure the appropriate IRB approvals.
 3. The investigator must submit all approved documents to the Reliance Form in eCompliance, including the fully executed authorization agreement and IRB approved documents, including the IRB approval letter. The MU IRB file in eCompliance should mirror the IRB of Record approval.
 4. The MU IRB reserves the right to require changes to local documents, including the consent, recruitment materials, and other materials. The MU IRB will work with the local investigators to make such changes.
 5. All local investigators engaged in the research must be listed on the IRB application and complete required IRB training.
 6. The MU IRB office will ensure all institutional requirements are met prior to local IRB acknowledgement allowing MU engagement in the research to begin, including but not limited to, including appropriate injury language in the consent, investigational pharmacy approval, etc. Refer to the Initial Review SOP for institutional reviews.
 7. When the IRB of Record will not review HIPAA waiver/alteration requests, or when the MU IRB determines local review is necessary, the MU IRB will review local HIPAA alteration and waiver requests.
 8. The investigator must comply with all stipulations outlined in the IRB Acknowledgement Letter regarding post-initial approval local reporting requirements.
 9. MU IRB may request a Site Initiation Visit prior to subject enrollment to ensure all processes are in place to successfully carry out the study. Notification in writing will be sent to the investigator if this is required. MU IRB may also conduct post-approval monitoring when necessary.
 10. Additional responsibilities are outlined in the study specific Authorization Agreement.

IRB Review Fees

The MU IRB implemented an IRB fee structure to cover costs of conducting the IRB review for some multi-site research projects and to cover costs for administrative reviews for serving as the relying IRB. The fee schedule is managed and maintained in the IRB office and is available upon request. The MU IRB office will work with investigators to budget accordingly.

Exempt Multi-Site Research

Exempt multi-site research is not subject to the requirements described above, except for exempt research falling under the limited IRB review provision. In order to track all multi-site exempt human subject research activities where another IRB already made an exempt determination, the IRB requests investigators submit the Collaborative Exempt Notification Form to document these activities. The form will be acknowledged in eCompliance unless it is determined that the IRB of Record made an incorrect determination according to the MU IRB interpretation of

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allowable exemptions. The MU IRB would request the investigator submit the MU IRB application in that case.

The MU IRB should not need to enter into authorization agreements on exempt studies, so a local IRB exempt determination is always an option for investigators. A few exceptions would be exempt studies reviewed under the limited IRB review provision, sponsor requires agreements, or other case-by-case situations where it is determined an agreement should be in place.

References:

Policy Revision Dates Prior to January 21, 2019:

June 10, 2010; July 1, 2011; March 1, 2015; July 1, 2015; June 8, 2017

Office for Human Research Protections (OHRP)

Engagement Guidance

Terms of the Federalwide Assurance of Protection for Human Subjects

IRB Knowledge of Local Research Context Guidance

Sample Unaffiliated Investigator Agreement

Food and Drug Administration (FDA)

Cooperative Research Guidance

Non-Local IRB Review Guidance

21 CFR parts 50 and 56

45 CFR 46.114