MCW Office of Research
Standard Operating Procedure

RELIANCE AGREEMENTS FOR MULTI-SITE PROJECTS

Unit: Human Research Protections Program (HRPP), Office of Research

Applies to: Faculty and Staff involved in human research

PURPOSE:
Medical College of Wisconsin (MCW) Institutional Review Boards (IRBs) provide oversight for all human subject research conducted by MCW/FH/Versiti/CW faculty, fellows, residents, staff or students. This policy describes efficient review mechanisms available for multi-site projects when research conducted by Medical College of Wisconsin, Froedtert Health, Versiti or Children's Wisconsin personnel is subject to parallel oversight by the IRBs of other institutions.

MCW has a robust reliance system which includes established relationships, procedures, and forms that assist in an efficient reliance decision. Local investigators must follow the established procedures in order to assure the effectiveness of this system.

Children's Wisconsin HRPP maintains oversight of projects involving Children's Wisconsin that require deferral to an external IRB.

DEFINITIONS:
Rely: Also known as *"defer or cede".* An institution agrees to transfer oversight of a project under its jurisdiction to another IRB. MCW requires a signed Agreement to be in place prior to final IRB approval of the project.

Engaged in Research: An institution becomes "engaged" in human subjects research when its employees or agents (all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility) (i) intervene or interact with living individuals for research purposes; (ii) obtain individually identifiable private information for research purposes, (iii) obtain informed consent from human subjects; or (iv) receive Department of Health and Human Services (HHS) funds even when all activities are carried out at another institution or by employees of another institution. The MCW or CW HRPP Director or designee will make the final determination regarding engagement in human subjects research, as applicable.

Federalwide Assurance (FWA): The only type of assurance currently accepted and approved by OHRP. Through the FWA, an institution commits to HHS that it will comply with the requirements in the HHS Protection of Human Subjects regulations at 45 CFR part 46.

Individual Investigator Agreement (IIA): An institution holding an OHRP-approved FWA may extend the applicability to cover two types of collaborating individual investigators when the project is federally supported: 1) collaborating independent investigator who is not otherwise an employee or agent of MCW, is conducting collaborative research activities outside of MCW, and is not acting as an employee of

any institution when conducting the research; 2) collaborating institutional investigator who is not otherwise an employee or agent of MCW, is conducting collaborative research activities outside of MCW, and is acting as an employee or agent of an institution that does not hold an FWA. This extension is documented using the Individual Investigator Agreement. The Director of the HRPP or designee will make the final decision regarding whether an IIA is appropriate for a specific case.

IRB Consortium: A group of IRBs that have established a working relationship with the goal of simplifying the IRB review process. In an IRB Consortium, a Master Reliance Agreement is signed and policies, procedures, and forms are developed which assist in implementing the reliance system.

Local PI: the MCW/FH/Versiti/CW investigator serving as the principal investigator (PI) at the local site.

Master Reliance Agreement: An Agreement that is executed between two or more institutions. The Agreement outlines scope, expectations and common requirements that will be followed. The Agreement is between institutions and IRBs, not between collaborating investigators. Master Reliance Agreement may be between institutions to establish an IRB Consortium or may be between an institution and IRB to establish IRB review and oversight for a collection of projects.

MCW IRB Oversight Jurisdiction: MCW defines the scope of oversight jurisdiction of the MCW IRB to include:

- Human subject research activities conducted at MCW.
- Human subject research activities conducted or initiated by MCW employees or agents at any other site.
- Human subject research activities that make use of any MCW resources other than faculty or employee time commitment.

All research projects meeting these criteria must by submitted to the MCW IRB for review and approval. If an investigator wishes MCW to rely upon a non-MCW IRB for review and approval of a project, the procedures outlined in the sections below must be followed.

Froedtert Health, Versiti and Children's Wisconsin have assigned the IRB review and approval of human subjects research to the MCW IRB. In addition, Froedtert Health and Versiti have assigned decisions to defer IRB review to an external IRB to the MCW HRPP. Children's Wisconsin HRPP maintains review and oversight of projects involving Children's Wisconsin resources and makes their own decisions when deferring to an external IRB is required and for a limited number of other projects. Questions regarding MCW IRB oversight jurisdiction should come to the MCW HRPP Office.

Multi-Site Project: A human subjects research project that will be initiated at more than one location other than or in addition to MCW. For examples of multi-site projects, see IRB SOP: *Multi-Site Projects and Investigator Responsibilities*.

Reliance Agreement/IRB Authorization Agreement/ Memorandum of Understanding: A formal, written legal document executed between two or more institutions which transfers IRB oversight from one institution to another IRB to consolidate IRB review. The Agreement is between institutions and IRBs, not between collaborating investigators.

Reliance System: A system developed by an HRPP Office which allows the institution to cede IRB oversight to another IRB or provide IRB review for a non-MCW institution. The system involves the use of policies, procedures, and forms that were developed to

simplify IRB review for a multi-site project where at least one non-MCW site is relying upon the MCW IRB or where MCW is deferring IRB oversight to a non-MCW site.

Relying Site: An institution where research will take place, but which will rely on an external IRB.

Reviewing IRB/ IRB of Record: The IRB responsible for review, approval and oversight of research involving a participating site or multiple participating sites.

Single IRB (sIRB): An IRB that oversees all sites participating in a multi-site project.

PROCEDURE:

1. All IRB reliance requests must be initiated via the appropriate reliance pathway as noted in the following sections.
2. All reliance requests are reviewed by MCW IRB Reliance in the order in which they are received.
3. Principal Investigators (PIs) should be aware that there may be cases where a reliance request is denied. Therefore, the MCW HRPP encourages PIs to submit the reliance request as soon as they can to avoid possible delays in IRB review.

Requests to rely on an outside IRB

1. The reliance pathway in eBridge should be used when a MCW/FH/Versiti investigator plans to participate in a multi-site project and would like to request that MCW rely upon a non-MCW IRB.
    a. In the SmartForm section for Project Category, choose 'Research Project requesting reliance on another IRB'
    b. Answer all questions and upload all documents prompted by the SmartForm.
2. When the MCW Reliance Team is notified of a request to rely on another IRB, staff will review the information, contact the PI for any additional information needed, and contact the appropriate HRPP Office regarding the proposed reliance request. Teams should allow 2 weeks for initial intake and review.
3. The local investigator must provide the IRB approval letter for involvement of this site when received.

Requests for a single site to rely upon the MCW IRB for review

1. The *Investigator Reliance Request Form* should be completed and sent to the MCW HRPP Office along with a copy of the protocol or narrative, if applicable. These documents must be provided to the MCW HRPP Office before the request will be considered.
2. When the MCW Reliance Team is notified of a request to serve as the reviewing IRB, staff will review the information, contact the PI for any additional information needed, and determine if the request is appropriate. If there is a decision to move ahead with the request, staff will contact the relying institution directly.
3. If the MCW IRB agrees to provide IRB review for an outside institution, additional information in the eBridge SmartForm and in the protocol must be provided as described in the IRB SOP: *Multi-site Projects and Investigator Responsibilities*.
4. In addition to the above, the local investigator must provide the following information in the protocol regarding local context <u>for any site that is relying upon the MCW IRB</u>:
    a. A completed Local Context Form
        i. MCW HRPP Office may waive this requirement if the relying institution is one of the institutions within the SEWIC CTSI partnership
    b. The CV for each relying site's lead investigator must be uploaded in the eBridge SmartForm application.

        i. MCW HRPP office may waive this requirement if the investigator is a faculty member of one of the institutions within the SEWIC CTSI partnership.
    c. Specific research activities to be conducted at that site
    d. Available resources for each relying site's lead investigator must be described in the protocol or addendum to the protocol
    e. Whether the relying site's research team will review records to determine eligibility
    f. Recruitment procedures to be conducted
    g. Consenting procedures to be conducted
    h. Confidentiality measures
    i. If project involves a drug, device, or biologic, where these will be stored, who will dispense them, and who will manage them
    j. The relying site's plan for evaluating and responding to subject complaints and reporting UPIRSOs to the MCW IRB
    k. Age of majority in the relevant state (if minors will be recruited)
    l. Explanation of any state or local laws governing the conduct of research
    m. Any cultural concerns in the local community

Requests for MCW to serve as single IRB

NIH has mandated the use of single IRB for certain types of NIH-supported non-exempt multi-site human subject research projects. Additionally, the revised Common Rule includes a single IRB requirement, which applies to non-exempt multi-site human subjects research projects funded by a Common Rule agency [45 CFR 46.114(b)].

NOTE: There is a fee for MCW to serve as sIRB for a multi-site project. This fee can be incorporated into a funding application. MCW IRB Reliance recommends reaching out to discuss a project before your grant application is submitted.

1. The *Single IRB (sIRB) Investigator Reliance Request Form* should be completed and sent to the MCW HRPP Office along with a copy of the protocol or narrative. These documents must be provided to the MCW HRPP Office before the request will be considered.
2. When the MCW Reliance team is notified of a request to serve as the sIRB, staff will review the information, contact the PI for any additional information needed. The request will then be routed to MCW HRPP leadership for consideration and for development of a fee quote for sIRB service. The quote will be sent to the PI for consideration.
    a. Research teams should allow one to two weeks for review of their request and generation of the fee quote.
3. If the MCW research team accepts the quote, a letter of permission will be generated, if needed, which may be included in a grant submission.
4. Once the research team is ready to move ahead with the request, Reliance staff will create a sIRB Package, which the MCW research team will route to the participating sites for review and signature.
5. If the MCW HRPP agrees to provide IRB review for an outside institution, additional information in the eBridge SmartForm and in the protocol must be provided as described in the IRB SOP: *Multi-site Projects and Investigator Responsibilities.*
6. In addition to the above, the local investigator must provide the following information in the protocol regarding local context for each site that is relying upon the MCW IRB:
    a. A completed Local Context Form
        i. MCW HRPP Office may waive this requirement if the relying institutions are within the SEWIC CTSI partnership

b. The CV for each relying site's lead investigator must be uploaded in the eBridge SmartForm application
    i. MCW HRPP Office may waive this requirement if the investigator is a faculty member of one of the institutions within the SEWIC CTSI partnership
c. Specific research activities to be conducted at that site
d. Available resources for each relying site's lead investigator must be described in the protocol or addendum to the protocol
e. Whether the relying site's research team will review records to determine eligibility
f. Recruitment procedures to be conducted
g. Consenting procedures to be conducted
h. Confidentiality measures
i. If a project involves a drug, device or biologic, where these will be stored, who will dispense them and who will manage them
j. The plan at the relying site for evaluating and responding to subject complaints and reporting UPIRSOs to the MCW IRB
k. Age of majority in the relevant state (if minors will be recruited)
l. Any cultural concerns in the local community

Requests to initiate an Individual Investigator Agreement (IIA)

1. An Individual Investigator Agreement can be requested of MCW when <u>all</u> of the following are met:
    a. the project is federally supported and will be conducted under the direction and supervision of a local investigator;
    b. the collaborative investigator will be engaged in research activities outside of MCW, FH, Versiti or CW;
    c. the MCW IRB is the reviewing IRB;
    d. non-MCW/FH/Versiti/CW research staff are employed by an institution that does not have an FWA, OR are not acting as an employee of any institution with respect to his or her involvement in the research; and
    e. the collaborating investigator is not affiliated with MCW, FH, Versiti or CW.
2. This mechanism does not apply if the collaborating investigator's institution is the primary awardee of federally funded human subject research.
    a. The MCW/FH/Versiti investigator should contact the MCW HRPP Office in this case to discuss how to proceed.
3. In order to initiate a request for an Individual Investigator Agreement, the MCW/FH/Versiti investigator must make the request via email to the MCW Reliance Team, along with:
    a. The protocol or the MCW IRB submission number (PROxxxx),
    c. Evidence of the collaborating investigator's completion of human subject research protection (HSRP) training,
    d. A letter of support from the collaborating investigator's institution if the collaborating investigator is an employee or agent of that institution. This letter of support must state that the institution is aware and supports the research activity taking place at their site. The letter of support is not required if a letter of support has already been provided with the grant proposal.

Consent forms for multi-site projects when a Reliance Agreement is involved

1. In all cases, the proposed consent form (if applicable) will need to be provided to the MCW HRPP Office.
2. **When the MCW IRB is the reviewing IRB**, the appropriate MCW consent form template must be used. Consent form templates can be found on the IRB website. Template change requests will be required for any changes not allowable per the

template. Template change requests should be submitted to the MCW HRPP Office for review and not to the MCW Reliance team.

a. The local investigator must provide the consent form for a non-MCW site for review and approval prior to use.
b. The MCW IRB will review, approve and stamp the consent form to be used at the non-MCW site. This consent form must be used by the non-MCW site to enroll subjects.

When MCW has deferred oversight to another IRB, the appropriate MCW consent form language for deferred projects must be included in the sponsor's or lead site's template. Consent form templates can be found on the IRB website. Template changes requests will be required for any changes not allowable per the template. Template change requests should be submitted to the MCW HRPP Office for review and not to the MCW Reliance team

Local Changes for multi-site projects when a Reliance Agreement is involved

1. **When MCW IRB is the reviewing IRB**, please refer to the *IRB SOP: Amendments*
2. **When MCW has deferred oversight to another IRB**, submit the following items in eBridge using the 'Request Local Change' activity:
    a. Change in PI
    b. Significant updates intended to keep the SmartForm current
    c. Requesting review of a new consent form
    d. Requesting review of a revised consent form that updates to the MCW templated sections
    e. Requesting changes to the methods of consenting
    f. Significant changes in the involvement of MCW/FH/Versiti
    g. Changes related to access of Protected Health Information (PHI), such as adding screening medical records for recruitment or adding the use of medical records

    The MCW IRB does NOT need or want every protocol amendment for a project. These should only be submitted to the IRB of record for approval.

    Updates to project team should be made in eBridge using the 'Update My Project' activity.

Reportable Events for multi-site projects when a Reliance Agreement is involved

1. **When MCW IRB is the reviewing IRB,** please refer to the *IRB SOP: Requirements for Reporting to the IRB.*
2. **When MCW has deferred oversight to another IRB,** submit events in eBridge using the 'Open New Reportable Event' activity. Only events which meet the prompt reporting criteria must be reported to MCW within 5 calendar days per *IRB SOP: Requirements for Reporting to the IRB.* These events generally include:
    a. Unanticipated problems involving risks to subjects or others (UPIRSO) that occur locally
    b. Notice from the sponsor or DSMB/Safety Committee that describes new information regarding risks or unanticipated problems involving risks to subjects or others (UPIRSO)
    c. Serious or continuing noncompliance
    d. Suspensions or termination of research

    Other events do not need to be reported to the MCW IRB such as anticipated adverse events, minor deviations, or miscellaneous reports. These only need to be reported to the IRB of record per their policies.

Closing a project when a Reliance Agreement is involved

1. **When MCW IRB is the reviewing IRB,** please refer to the *IRB SOP: Project Closure.*
2. **When MCW has deferred oversight to another IRB,** notify the MCW HRPP of project closure at this site using the eBridge 'Request to Close Project' activity.

Investigator Responsibilities

Local PIs must follow the IRB SOP: *Responsibilities for Investigators Conducting Human Subject Research* and IRB SOP: *Multi-site Projects and Investigator Responsibilities*.

In addition to the responsibilities outlined in these policies, local PIs using the reliance system must also comply with the responsibilities listed below:

Investigator Responsibilities when the MCW IRB is the Reviewing IRB

1. Ensure that human subject research activities do not begin at any relying site until IRB approval is obtained in writing from the MCW IRB.
2. Submit an amendment to the IRB when adding site(s) to a project that has already been approved by the MCW IRB. The amendment should revise the protocol and SmartForm to include:
   a. Addition of the site(s),
   b. Explanation of research activities to be conducted at the site(s),
   c. Research activities to be conducted by employees of the site(s) and where they will be conducted.
3. Include PI and primary research coordinator from the relying site(s) in the SmartForm. If there are changes to these individuals during the course of the project, these changes should be reported to the MCW IRB.
4. Ensure that investigators at the relying site(s) receive a copy of the IRB approval letter, approved protocol, consent form, and other documents (if applicable).
5. Notify investigators at relying sites of all MCW IRB determinations and communications, including those for initial review, continuing review, amendments and reportable events.
6. Upon request, provide access to records for audit or routine review by the MCW IRB.
7. The MCW/FH/Versiti/CW PI is responsible for gathering progress report information from relying sites, collating information, and providing a status report for each relying site in the Continuing Progress Report to the MCW IRB. If the MCW/FH/Versiti/CW PI is the Principal Investigator for the entire project, the progress report must also include the status of the overall project.

Investigator Responsibilities when a non-MCW IRB is the Reviewing IRB

1. Conduct the project in full compliance with the Federal Wide Assurances (FWA), institutional policies of the Medical College of Wisconsin, Froedtert Health, and Versiti and applicable federal and state regulations.
2. Ensure that human subject research activities do not begin until final documentation of reliance has been received and the project has been approved in writing by the IRB of record.
3. Employ and assume the responsibility for the informed consent process in order to ensure that potential research subjects understand the purpose of the project, the procedures they are being asked to undergo, the potential risks, benefits, and alternatives of the project, their rights as a research subject and have sufficient time to decide about participating. Do not enroll any subject in the project or conduct project procedures until such informed consent is obtained, unless waived by the IRB of record.
4. Ensure that subjects are kept fully and promptly informed of any new information that may affect their willingness to continue to participate in the project.

5. Maintain current and accurate records of data, outcomes, and adverse events to permit an on-going assessment of the risks/benefits of participation. Ensure the privacy of subjects and maintain the confidentiality and security of the data in accordance with *IRB SOP: Privacy and Confidentiality*.
6. Report to the IRB of record and the MCW HRPP in a timely manner all unanticipated problems involving risk to subjects or others (UPIRSOs), serious and/or continuing non-compliance, and suspension or terminations.
7. Make a reasonable effort to ensure that subjects who have suffered an adverse event associated with research participation receive adequate care to correct or alleviate the consequences of the adverse event to the extent possible.
8. Provide site information to the Lead Principal Investigator (PI) so they can submit the project in a timely manner for the "Continuing Progress Review", when applicable, in order to obtain IRB renewal/approval from the IRB of record. Be aware that failure to do so, when necessary, will result in a lapse of project approval and all project activities must stop.
9. Agree to follow the protocol as approved by the IRB of record. All protocol deviations will be reported to the IRB of record. Documentation of protocol deviations will be kept in the project regulatory files, and if applicable, in the subject's research files.
10. Ensure that the research coordinator(s), co-investigator(s) and other research staff understand their association with and role in the project. Provide access to a copy of the project protocol for the research coordinator(s), co-investigator(s) and other research staff. Also ensure that all members of the research team have complied with the MCW Human Subject Research Protection training requirements as described in *IRB SOP: Human Subject Research Protections Training Requirements.*
11. Identify and disclose all actual or perceived conflicts of interest in accordance with *IRB SOP: Conflicts of Interest for Investigators and Project Team Members.*

<u>Investigator Responsibilities when using an Individual Investigator Agreement</u>

1. Assure that the collaborating investigator has complied with all stipulations in the Agreement for reviewing *The Belmont Report*, the HHS regulations and relevant institutional policies and procedures for the protection of human subjects.
2. Assure that the collaborating investigator has completed HSRP training required by MCW per *IRB SOP: Human Subject Research Protections Training Requirements*.
3. When the IIA has been executed, submit an amendment to the MCW IRB to add the collaborating investigator to the project.

REFERENCES:

45 CFR 46

SUPPORTING DOCUMENTS:
IRB Form: Investigator Reliance Request Form
IRB Form: sIRB Investigator Reliance Request Form
IRB SOP: Responsibilities for Investigators Conducting Human Subject Research
IRB SOP: Multi-site Projects and Investigator Responsibilities
IRB SOP: Amendments
IRB SOP: Requirements for Reporting to the IRB
IRB SOP: Project Closure
IRB SOP: Human Subject Research Protections Training Requirements
IRB SOP: Conflicts of Interest for Investigators and Project Team Members.
MCW IRB Reliance Consent Form Guidelines
The Belmont Report

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