Guidance
Multi-Site Projects and Investigator Responsibilities

Purpose

The purpose of this guidance document is to:

- Describe considerations and expectations for research that involves multiple centers, including studies involving Children's Wisconsin (Children's) and MCW/FH/Versiti;

- Help the protocol development process and avoid delays and additional questions during Local Context and IRB review.

There are several possible scenarios when this guidance applies:

- A protocol where research interventions are to be carried out by investigators at more than one institution (e.g., obtaining consent, interacting or intervening with subjects, administering research interventions). Consistent with both CW HRPP SOP manual and MCW IRB policy entitled *Multi-Site Projects and Investigator Responsibilities*, this includes research being conducted at Children's in addition to MCW/FH/Versiti. Children's is a legally separate entity from those institutions and as such, these studies are considered to involve multiple sites.

- A protocol where a Children's investigator is conducting research at one or more locations not under the control of Children's (for example, schools; community centers, other healthcare facilities, etc.).

- When a Children's investigator is sharing identifiable information collected for a research study with investigators at another institution.

- When a Children's investigator is receiving identifiable data or specimens provided by an investigator at another site to be analyzed for the purpose of answering a research question.

- When a study was initially a single site study but is being amended to add additional sites, thus making it a multi-site study (CW single site study adding FH/MCW/Versiti, or adding CW to a study already approved at MCW/FH/Versiti).

This guidance **does not** apply to:

- Studies being conducted at multiple Children's locations that fall under the jurisdiction of the Children's HRPP (for example, Children's Main Hospital and Children's Midtown Clinic).

- Studies involving the sharing of de-identified data or specimens with collaborators at other entities (this is generally considered not to meet the definition of human subjects research, provided that the details are described in the IRB approved protocol). There is a different process for requesting a determination that a project is not human subjects research (for

details to request a determination contact the CW HRPP office at CWHRPP@childrenswi.org .

Note: Specific details would need to be provided to obtain guidance from the Children's HRPP to determine whether this guidance applies and to help with for submission of a project.

DEFINITIONS

What is a multi-site or collaborative research project and what does it involve?

NIH uses the term "**multi-site project**" to describe a sub-set of cooperative non-exempt human research where the same research procedures (i.e., the "same protocol") are conducted at two or more U.S. research sites under the control of a participating local site investigator at each site.

A multi-site project typically involves a lead site (lead PI) that manages the administrative functions of the project in addition to conducting the same research procedures at the participating sites. A multi-site project could be a clinical trial, an observational study, or a basic clinical research study.

For the purposes of this guidance, Children's is a separate location (institution) from Froedtert Hospital, Versiti, or MCW. **A study would be considered a multi-site research project if Children's is being added to a study already being conducted at Froedtert Hospital, Versiti, or MCW.**

A "**cooperative**" (or "**collaborative**") project involves two or more research sites where each site is conducting a different part of a research protocol under the direction/control of the lead PI. An example would be a non-exempt study where CW is the lead site and conducting the interaction/intervention with the human participants, but the analysis of the data is being done by an external institution/collaborator.

A plan must be developed in advance that describes the managing or leading of an investigator-initiated multi-site study in order to enhance the ethical performance of the research study, ensure the appropriate oversight and conduct of the research study, and to promote the accuracy and quality of research data collected.

Lead Site or Coordinating Center an individual or group of individuals responsible for oversight and management of the conduct of a multi-site study at all collaborating intuitions. A coordinating center may be designated by the study sponsor or by mutual agreement among participating sites.

The terms are often used interchangeably and are terms that encompass the entity responsible for overall data management, monitoring and communication amongst all participating local sites, and general oversight of the conduct of a research project involving human subjects at multiple locations. Responsibilities associated with serving in the capacity of a lead site will depend on the type of research and level of risk to subjects.

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Lead Principal Investigator (PI) is the individual with primary responsibility for oversight and management of the conduct of the study at all participating research sites.

As part of the application to include Children's, the lead site and lead PI for the project must be identified.

An **Overall IRB of Record**, if there is one, (also known as a "Central IRB," "External IRB," "Reviewing IRB," "Designated IRB," or "Single IRB") is the reviewing IRB that assumes responsibilities for IRB regulatory determinations and oversight on behalf of another institution. This designation is established through a reliance agreement (also known as a "reliance," "deferral," or "IRB Authorization Agreement" (IAA)). For federally-funded research, all institutions engaged in research must have a current Federalwide Assurance (FWA) with OHRP (Office for Human Research Protections). In the case of research taking place on campus, MCW IRBs serve as the primary IRB of record for Children's under an executed IRB research agreement and an individual agreement does not need to be negotiated.

Note: A lead site's IRB may serve as the overall IRB of record for a study; however, this is not always the case. Alternatively, each institution may have local IRB approval (if not subject to the requirement for single IRB oversight) or rely on the IRB review services of another institution's IRB.

Local Site PI is the individual at each site who agrees to participate in the multi-site study and is responsible for the oversight of the conduct of the study at his or her institution.

HRPP is defined as a shared responsibility for the welfare of subjects in research, involving multiple components, filling in the myriad gaps surrounding the jurisdiction of the IRB. With all such components interconnected properly, a "safety net" is formed to help ensure the optimal protection of the rights and welfare of the subjects. The CW HRPP office helps to ensure all of the components operate efficiently to protect human subjects.

Local Context means applicable state or local laws and regulations; institutional policies and requirements, standards, or other local factors including local ancillary reviews and restrictions on use and disclosure of PHI; investigator and study team experience; local community and subject attitudes; and institutional consent language requirements, which will need to be considered for the institution where the research is conducted, and addressed during the review process by the designated IRB of record. This may include federal laws and regulations other than human subjects protection regulations that are relevant to a research study for which review is being ceded under the Agreement.

During local context **review**, these items are taken into consideration for each specific study being conducted in Children's space. The HRPPs for the other institutions involved in the research will conduct their own local context review.

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Does my multi-site study involving MCW/FH/Versiti and CW require one submission or two submissions in eBridge?

Ideally, the CW HRPP will be consulted prior to any submission to determine the best pathway.

If it is submitted as one submission without consultation, CW HRPP may still determine that a separate submission is required. Contact the CW HRPP to discuss the specifics of the protocol well prior to submission. The answer will depend upon the details of the study.

- The more activities that are occurring at CW, the more complicated the procedures, when two separate study teams are managing the research activities, the more likely it will require a separate CW submission.
- Regardless of whether it is one or two submissions, an appropriately qualified Children's PI must be identified that meets *CW policy requirements*.
- The eBridge PRO must indicate "multi-site" study and PRO completed appropriately (see below).
- The lead-site study protocol must document in detail what will be conducted at each site.

***IMPORTANT:* If you are amending a study that now would like to engage Children's, the above points apply. It is highly recommended to contact the Children's HRPP Office for guidance before submitting the amendment in eBridge to determine feasibility.** *The Children's HRPP can identify what should be described in the application as well as considerations and department sign offs that need to be in place prior to submission. The Children's HRPP will also ensure that the project will be reviewed by an appropriately constituted IRB with pediatric expertise. The Children's HRPP must ensure appropriate local context review and regulatory oversight of the pediatric population (e.g., oversight by an appropriate local site investigator, involvement of coordinators knowledgeable about working in Children's space, review by the appropriate Pediatric Specialty IRB Committee).*

What are Children's requirements for multi-site projects?
If Children's is only a participating center (most frequent scenario):

- The eBridge PRO must indicate that the project activities will take place at more than one site.
  - This is selected in Section 3.3 and will trigger Section 7 "Multi-Site Project"
  - For the purposes of Children's Local Context review, you must select NO for question 7.1; this will then trigger a table which must define the specific activities taking place at each site.
- There must be a CW qualified local site PI to oversee all activities occurring at Children's. The local site PI can be identified through:
  - The PI listed in eBridge if there is a separate CW submission, or

- a signed attestation by the local PI included in Section 52 if a single submission is deemed appropriate.

In addition, if Children's is acting in the capacity of **both** the lead site and a participating center conducting the research, the protocol must describe the separate responsibilities of the lead site as well as the activities of the Children's participating local site.

GENERAL CONSIDERATIONS FOR A MULTI-SITE STUDY

The study-wide protocol must outline the responsibilities of the lead site and the lead PI.

- The protocol must address how the lead PI and lead site will assume responsibility for the overall conduct and management of the study, addressing the responsibilities listed below.
- This information may be embedded within the main study protocol or provided as a separate addendum/Manual of Operations (MOO).
- The location of the information is not as important as having the information included somewhere in the application in sufficient detail for evaluation.
- When the Children's HRPP reviews a submission, depending on the lead site's stated responsibilities, the Children's HRPP must be able to determine that the lead site has a sufficient plan in place for study management pertinent to the research.

In developing the protocol (or coordinating center lead site-specific addendum/MOO), consider and address the following (as applicable):

- What is the organizational structure of the lead site?
    - Are there separate individuals or groups responsible for administrative duties, protocol development, local site monitoring, safety monitoring, data analysis, etc.?
    - Will any responsibilities be delegated to other institutions or agencies (for example, data management or specimen storage)? If so, the responsibilities allocated to separate committees and/or entities must be clearly identified.
- What training will be provided to participating local site staff?
    - Will there be study meetings, teleconferences or training sessions required for staff at participating local sites prior to protocol implementation and throughout the course of the study?
- How will the lead site develop and distribute approved study documents (sample consent/template, study-wide protocol, worksheets/data collection tools, surveys/questionnaires,

case report forms, IRB approvals, etc.) to participating local sites as they become available or are revised?

- How will the lead site manage and/or monitor each participating local site's study conduct including:
    - Consenting, enrollment, research procedures, data collection, data storage/security, research subject privacy/confidentiality, withdrawals and reporting of unanticipated problems and protocol violations/deviations (and ensure they are in compliance with federal regulations and IRB approval)?
    - How will participating local sites be expected to report this information to the lead site?
    - Will monitoring visits be conducted? If so, how often? Will visits be conducted in person or online? What will the monitoring visits entail?
- How will the lead site ensure participating local site consents/assents/protocols are consistent with the lead site templates/overall protocol/example documents?
- If participating local site consents/assents/protocols are substantially modified (such as risk/alternative procedures etc.), how will the lead site ensure that these modifications are appropriately justified and will not adversely affect the study design?
- How will the lead site track, report and maintain documentation of reports of all serious adverse events and unanticipated problems, and disseminate pertinent information to participating local sites?
- How will the lead site provide periodic updates regarding subject enrollment, general study progress, interim results, and any significant new information?
- How will the lead site ensure that the participating local sites have an applicable OHRP-approved Federalwide Assurance (FWA) (if the study is federally funded) and ensure that the participating local site's IRB approval is issued prior to start of study activities and that IRB approval does not lapse (if the study does not involve reliance on a single IRB)?
- If biologic specimens are involved, how will the lead site document receipt and how will the participating local site be expected to document shipment/storage?

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- If investigational products (drugs/devices/biologics) will be used, how will they be provided to each participating local site?
    - How will dispensing be monitored?
    - What investigational product accountability procedures will be implemented?
    - How will randomization occur and be tracked?
- What are the procedures for study closures, early center voluntary closures, and suspensions or terminations due to noncompliance?
    - How will these be reported to the participating local site's IRB?

Will Children's HRPP consider ceding IRB oversight to an IRB other than the MCW pediatric IRB?
Yes, in limited circumstances, although it depends on the nature of the study and the study activities to be conducted at Children's, and whether single IRB review is mandated by federal regulations. Please contact the Children's HRPP early in the discussion phase and prior to any formal submission in eBridge.

Does Children's have standing agreements with other institutions in addition to MCW?
Yes, Children's IRB has the following agreements in place that may assist researchers in conducting multi-site and collaborative research (this list is not exhaustive of all agreements in place):

- Agreement with the NCI CIRB for some NCI and NMDP studies involving adult and pediatric subjects.
- Children's HRPP has signed the joinder agreement for SMART IRB, which is not an IRB, but rather, a ceding platform. SMART IRB facilitates the use of a Master Reliance Agreement that provides a central process for participating institutions to request, track and document study-specific reliance arrangements. Decisions to rely using the SMART IRB platform is preferred, but is not automatic and is made on a study-by-study basis.

Does the Local Context review process take longer for multi-site studies?
Depending on the proposed IRB of record, the complexity of the study and the quality of the coordinating center application and study protocol, the local context review process may take additional time. A well-prepared application and study protocol can help to ensure that the local context and IRB review processes go as smoothly as possible. Staff in the Children's HRPP office are available for consultation at any time during the protocol development phase, but only as it relates to reliance and submission, not to assist with scientific or scholarly design.

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Children's HRPP continues to develop additional resources to aid in these types of studies, and this guidance may be updated periodically. If you have any questions about multi-site research, please contact the HRPP Office at (414) 337-7133 or via email at cwhrpp@childrenswi.org.