Guidance
Conducting Investigator-Initiated Multi-Center Collaborative Research Activities

This guidance generally applies to research where the investigator, under oversight of the Children's Wisconsin Human Research Protection Program (Children's HRPP), is responsible for the overall conduct of the study. That is, the investigator is the lead investigator of a multi-center study or provides study-wide services, such as for data coordination. [AAHRPP element II.2.I]

Purpose

The purpose of this guidance document is to:

- Describe considerations and expectations for investigator-initiated research (research not sponsored by industry or an established cooperative group such as COG, NMDP, etc.) that involves multiple centers;

- Describe the expectations for data management when a Children's or Medical College of Wisconsin (MCW) investigator serves as the coordinating center Principal Investigator (PI), or when Children's is responsible for the Coordinating Center activities;

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

There are several possible scenarios to which this guidance applies:

- An investigator-initiated 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).

- A protocol where a Children's/MCW 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/MCW investigator is sharing identifiable information collected for a research study with investigators at another entity.

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

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This guidance **does not** apply to:

- Studies being conducted at multiple Children's locations that fall under the jurisdiction of the Children's IRB (for example, Children's Main Hospital and Children's Midtown Clinic);
- Multi-center clinical trials conducted by an industry sponsor or an established cooperative group;
- Studies involving multi-center research where Children's is BOTH the coordinating center and the IRB of Record (while this guidance will aid in coordinating center setup, there are additional items that need to be considered when Children's serves as the IRB of Record AND the coordinating center);
- Studies involving the sharing of de-identified data or specimens with collaborators at other entities (this is not considered human subject research, provided that the details are described in the IRB approved protocol).

Note: Specific details will be required to provide further guidance on next steps.

What is multi-center research and what does it involve?
"**Multi-center**" research refers to research that is written to include conduct of a model protocol carried out at more than one institution.

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

A **Coordinating Center** is the term used to refer to the entity responsible for overall data management, monitoring and communication amongst all participating centers, 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 coordinating center will depend on the type of research and level of risk to subjects. A coordinating center may be designated either by a sponsor or by mutual agreement of the participating centers.

As part of the application to Children's, the coordinating center and the coordinating center PI for the project must be identified.

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An **Overall IRB of Record**, if there is one, (also known as a "Central IRB," "Reviewing IRB," "Designated IRB," or, "Single IRB") is the reviewing IRB that assumes responsibilities for IRB determinations and oversight on behalf of another institution. This designation is established through a reliance agreement (also known as a "deferral" or "IRB Authorization Agreement" (IAA)). For federally-funded research, all centers engaged in research must have a current Federalwide Assurance (FWA) with OHRP (Office for Human Research Protections).

Note: A coordinating center'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).

What are Children's requirements for multi-center collaborative research?
If Children's is acting in the capacity of both a coordinating center and as a participating center conducting the research, two separate applications must be submitted to the IRB (two IRBNet numbers):

- An application that outlines the responsibilities of the coordinating center (coordinating center application); and,
- An application that describes the activities of the Children's site (participating center application).

Contact the HRPP Office for guidance before submitting the proposal. Depending on the complexity of the study, if only two centers will be participating, the IRB *may not* require the submission of a separate coordinating center application.

The **coordinating center application** and study-wide protocol outlines the responsibilities of the coordinating center and the coordinating center PI. The protocol must address how the coordinating center PI and coordinating center 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 (MOP). When the Children's IRB reviews a coordinating center application, depending on the center's stated responsibilities, the Children's IRB must be able to determine and document that the center has a sufficient plan in place for study management pertinent to the research. In developing the protocol (or coordinating center specific addendum/MOP), consider and address the following (as applicable):

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- What is the organizational structure of the coordinating center?
    - Are there separate individuals or groups responsible for administrative duties, protocol development, center 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 center staff?
    - Will there be study meetings, teleconferences or training sessions required for staff at participating centers prior to protocol implementation and throughout the course of the study?
- How will the coordinating center ensure that appropriately qualified participating centers and Participating Site Principal Investigators are selected and appropriate documentation of local context considerations is on file (for example, resume/CV, medical license, certificate of completion for human subject protection training; laboratory certifications and laboratory normal ranges; conflicts of interest disclosures and management plans, if any; administrative approvals; etc.)?
- How will the coordinating center 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 centers as they become available or are revised?
- How will the coordinating center manage and/or monitor each center'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 centers be expected to report this information to the coordinating center?

  - 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 coordinating center ensure participating center consents/assents/protocols are consistent with the coordinating center templates/overall protocol/example documents?

- If participating center consents/assents/protocols are substantially modified (such as risk/alternative procedures etc.), how will the coordinating center ensure that these modifications are appropriately justified and will not adversely affect the study design?

- How will the coordinating center track, report and maintain documentation of reports of all serious adverse events and unanticipated problems, and disseminate pertinent information to participating centers?

- How will the coordinating center provide periodic updates regarding subject enrollment, general study progress, interim results, and any significant new information?

- How will the coordinating center ensure that the participating centers have an applicable OHRP-approved Federalwide Assurance (FWA) (if the study is federally funded) and ensure that the participating center's IRB approval is issued prior to start of study activities and that IRB approval does not lapse?

- If biologic specimens are involved, how will the coordinating center document receipt and how will the participating center be expected to document shipment/storage?

- If investigational products (drugs/devices/biologics) will be used, how will they be provided to each participating center?

  - How will dispensing be monitored?

  - What investigational product accountability procedures will be implemented?

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  - 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 center IRB and the Children's IRB?

The **participating center application** and protocol submitted by the participating site PI will serve to outline the local conduct of the research with participants at Children's.

If Children's is the coordinating center and a participating site, then two continuing reviews will need to be submitted to the Children's IRB.

- One that addresses study-wide and overall coordinating center activities (all participating centers' information such as accrual and withdrawal numbers, unanticipated problems, subject experiences, etc.); and,

- One that addressed the conduct of the local Children's participating site.

Will Children's consider serving as the overall IRB of Record?
It depends, and in limited circumstances. The Children's IRB must fully understand Children's and the Children's/MCW investigator's role in these activities before making a decision. Depending on the nature and complexity of the study and the activities that will be conducted at non-Children's centers or by non-Children's personnel, it may not be feasible for the Children's IRB to serve as the IRB of Record for a multi-center study at this time.

If the Children's IRB is being asked to serve as the IRB of Record for such activities, this must be discussed with the Research Integrity Manager and approved well in advance of the submission. The decision is made on a site-by-site basis and may be different for sites within the same study. Some considerations include:

- Does the site have an active HRPP with monitoring capabilities?
- Is the site AAHRPP accredited?
- Has the site signed the SMART IRB joinder agreement?
- Does the Children's HRPP have an established relationship with the site?

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You must also check with the participating centers' HRPP(s) as that may not be consistent with their policies

- Are there circumstances where the participating center will not require their own IRB approval?

Whether IRB approval is required depends on whether the non-Children's center or non-Children's personnel are engaged in human subject research. Most sites rely on OHRP guidance to make the assessment (see http://www.hhs.gov/ohrp/policy/engage08.html).

It also can depend on whether a study meets criteria for an exemption determination. Determining whether a non-Children's center or non-Children's personnel are engaged in human subject research or whether a research study meets exemption criteria can be difficult.

Researchers are encouraged to consult with the Children's HRPP Office by contacting (414) 337-7133 for guidance early in the protocol development process.

Will Children's consider ceding IRB oversight to another 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 submission to the Children's IRB if you would like to make such a request.

Please visit the HRPP Home page on Connect for instructions for how to initiate this request.

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

- Agreement with the NCI CIRB for some NCI studies involving adult and pediatric subjects.
- SEWIC (Southeastern Wisconsin CTSI IRB Consortium) Agreement with the following organizations: Versiti (formerly, The Blood Center of Wisconsin), the Medical College of Wisconsin, Milwaukee School of Engineering, Marquette University, the University of Wisconsin-Milwaukee, and Froedtert Hospital, which allows for a specific method of reviewing the appropriateness of ceding review via an Investigator Reliance Request Form.

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- 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 are not automatic, but made on a study-by-study basis.

Does the IRB review process take longer for multi-center studies?
Depending on the complexity of the study and the quality of the coordinating center application and study protocol, the IRB review process may take additional time. A well-prepared application and study protocol can help to ensure that the IRB review process goes as smoothly as possible. Staff in the HRPP 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.

Additional considerations

- An existing single site study that is being expanded to include multiple centers in which Children's will be the coordinating center will require:
    - An amendment to the existing project which converts the project to a participating center application (Children's as the participating local site location, same IRBNet number, new package)
        - This will now explain how the study is conducted at Children's
    - A new separate application providing the coordinating center considerations outlined in this guidance (New IRBNet number):
        - This must explain how the study will be coordinated by Children's across all centers
        - This application will be amended with additional packages to seek approval to add each participating center (the participating center may not be able to obtain their center's IRB approval without the coordinating center protocol approval by Children's IRB to include that site):
            - A subsequent "other" package should be submitted and include each participating center's IRB's approval letter once this is available

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- Reminder: each institution may have their own IRB oversight, this does not mean that Children's is the IRB of record (additional considerations would apply).

- The package should not contain any informed consent documents, HIPAA Authorizations, or participating center protocols because the Children's IRB is not the IRB of record for the participating center; it is the coordinating center PI's responsibility to verify and maintain these documents (which may be verified during an audit).

- A contract or data/material transfer agreement may be required. This will be considered during the administrative review process. You may also want to check with Children's Corporate Compliance in advance of the submission.

- IRB fees for review may apply.

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-center research, please contact the HRPP Office at (414) 337-7133 or via email at chwirb@chw.org.