Introduction to the Review Pathways

When a study meets the criteria to be considered Human Subjects Research (HSR), the study will fall into 1 of 3 categories for review: Convened Board, Expedited, or Exempt.

Convened ("Full") Board Review: A "full board" review is one that takes place at a convened meeting at which a majority of members must be present, including a member whose primary concern is in a non-scientific area, before official actions may be taken. In order for the research application to be approved, it must receive approval of a majority of those members present at the meeting. Approval of the project requires it meeting the regulatory criteria for approval found at 45 CFR 46.111 and 21 CFR 56.111 If a project does not meet regulatory criteria for expedited review or an exempt determination, it must be reviewed via this pathway.

Expedited Review: An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110 and 21 CFR 56.110. An expedited review happens outside of a scheduled meeting and does not need to be reviewed by the entire committee. "Expedited" does not mean that a project is getting a faster, a prioritized, or an abbreviated review. To qualify for an expedited review pathway, the research must meet regulatory criteria for one of the expedited categories (discussed below). Approval of the project requires it meet the regulatory criteria for approval found at 45 CFR 46.111 and 21 CFR 56.111. The expedited review categories are published in the federal register for FDA regulated studies and federally-funded studies and may be updated from time to time.

Exempt Research: Unless otherwise required by law or by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of defined categories are exempt from the requirements of regulatory policy, except that such activities must comply with the requirements of the regulations as specified in each category. Exempt studies do not require additional IRB oversight once the determination is made. To qualify for an exempt determination, the research must meet regulatory criteria for one of the exempt categories (discussed below). The regulations do not specify who at an institution may determine that research is exempt under 45 CFR 46.101(b). However, OHRP recommends that, because of the potential for conflict of interest, investigators not be given the authority to make an independent determination that human subjects research is exempt. At Children's Wisconsin, policy delegates this determination be made by the IRB of record as described in section 5 of the CW HRRP SOP manual.

This section is describing some specifics relative to the use of the MCW pediatric IRBs as the IRB of record. However, CW may choose to rely on other IRBs to serve as the IRB of record. In these cases, some of the specific details will differ and the policies of that IRB of record should be consulted.

GREATER THAN MINIMAL RISK RESEARCH

Full Board/Convened Board review:

What is Full Board/Convened board review?

For pediatric research, when a study meets the criteria to be considered **Greater than Minimal Risk**, the study must be reviewed by the convened board, to which it is assigned, during a regularly scheduled meeting, prior to approval. Some reasons that a study may require convened board review include:

- The study proposes to use procedures that may be intrusive, stressful, or potentially traumatic to the subject, therefore increasing risk.
- The study may involve intentional deception of subjects.

It is important to note that studies may have a combination of procedures/interventions that are Greater than Minimal Risk AND Minimal Risk. For example, a study may include administration of an investigational drug (which is a greater than minimal risk procedure) and medical record review (which is a minimal risk procedure). When this occurs, the study will still go to the convened board to make a determination. Of note, the convened board will make both the minimal risk and greater than minimal risk determinations for the same study (component analysis.)

While all studies that are greater than minimal risk will require review by the convened board, in some cases studies that qualify for expedited review may be brought to the convened board at the recommendation of the HRPP office or an IRB chair. This applies to any type of submission (new studies, reportable events, amendments, continuing review, etc.)

"Real Time" IRB review: Some studies being reviewed by the MCW Pediatric IRBs (this does not apply when CW is relying on a different IRB as the IRB of record) may qualify for "real time" review. The goal of Real-Time IRB review is to schedule new IRB submissions for review at an IRB committee meeting within 14-20 days from the day that they are received by the IRB All departmental and ancillary review(s) must be complete. See the MCW website for more information.

How is a Greater than Minimal Risk (Convened Board) study submitted to and reviewed by the IRB?

If any component of the research study presents a risk to the subject that is considered more than minimal risk, it must be reviewed at a convened meeting of the full board. The IRB of record makes the determination regarding project risk level.

Greater than minimal risk determinations that are made by the convened board fall into different pediatric risk categories, according to the federal regulations: a 45 CFR 46.405 determination will be made for studies that involve greater than minimal risk, but provide prospect of direct benefit to the subject(s), whereas a 45 CFR 46.406 determination will be made for studies that involve greater than minimal risk but do not provide prospect of direct benefit to the subject(s).

When MCW is serving as the IRB of record for research being conducted at CW, the Pediatric IRB Committee Board #8 will conduct these reviews. The current roster of members and the meeting schedule for this committee can be found here.

MINIMAL RISK RESEARCH

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 21 CFR 56.102 (23)(i) and 45 CFR 46.102(j)

Studies in which all components present no more than minimal risk study to subjects fall into 1 of 2 review categories: Expedited review or Exempt Review. Please see the sub-sections below for guidance on whether your study qualifies for expedited review or an exempt determination.

Expedited Review

What is Expedited Review?
When a study meets the one of the regulatory criteria for expedited review (one of which is that the project is considered solely **Minimal Risk**) the study can be reviewed by members of the IRB/HRPP without the need for convened board review. This means that rather than being reviewed by the entire committee at a regularly scheduled meeting, an IRB

chair, or committee member delegated by the chair, can review the project outside of the scheduled meeting.

The expedited reviewer can approve a project or request modifications. However, they cannot disapprove the project. If an expedited reviewer feels the project may be approval the project will be reviewed by the convened board to make that determination.

Note: "expedited" does not mean fast or that a project is given priority for a review. It means that the project meets the criteria to fall into one of the regulatory expedited review categories and is reviewed outside of a convened board meeting. If you would like to request that a submission, be prioritized, you will need to contact both the CW HRPP and MCW IRB. Both parties will consider the request and determine if the request can be accommodated

How is an expedited study reviewed by the IRB?
When a project qualifies for the expedited review pathway, it will be reviewed outside of a convened meeting by the IRB committee chair, or a qualified member of the committee delegated by the chair. Research reviewed via this pathway still need to meet the same regulatory approval criteria as research reviewed at a convened meeting.

When MCW is serving as the IRB of record for research being conducted at CW, the Pediatric IRB Committee Board #7 will conduct these reviews. The current roster of members and the meeting schedule for this committee can be found here. This committee has a schedule; however, it may not meet in a given month depending on whether a convened meeting is needed. While most reviews will be done by a delegated reviewer, there are some submissions that may be referred for review by the convened committee. This could be reportable events, projects for which the delegated reviewer or chair has particular concerns and would like the entire board to review, or other reasons as felt appropriate by the MCW/CW HRPPs or the committee.

In order for a research project to be reviewed via the expedited review pathway, it must fall into one of the regulatory expedited categories.

The initial determination of the appropriate review pathway will be made by the MCW HRPP office/CW HRPP office, and the project will be assigned to the appropriate Pediatric IRB Committee base on this assessment. However, the IRB has the final authority to determine what constitutes a minimal risk research study.

Expedited Review categories

Exempt Determination

What is Exempt Review?

Some types of human subjects research may be eligible for a determination that the project is exempt from the federal regulations requiring IRB review and oversight. The institution, not the investigator, makes the formal determination of whether a project meets the exemption criteria. (45 CFR 46.104(d) and 21 CFR 56.104,

The purpose of these exemptions is to minimize IRB oversight that may be unnecessary for certain studies and may provide some benefit to the public. If an institution makes a determination that a human subjects research project is exempt, then the additional federal regulations regarding human subject research do not apply to that project. However, this determination does not exclude the project from institutional requirements (including HIPAA regulations) that may apply.

The Common Rule federal regulations include eight exemption categories. In order for a research project to be exempt it must meet the criteria of one of these exempt categories.

OHRP has a decision charts available to assist investigators in assessing whether any of the exemption categories apply to their research. **NOTE however**, that the institution decides who will make the determination of whether or not a research project is exempt at that institution, particularly because institutions may have local policies about how the categories are applied to research in that institution. For example, in the context of collaborative research one institution may exempt a study while another institution may not.

Exemption categories that do not apply tro research involving children:

- **Category 2,** which addresses interactions with subjects in the form of tests, surveys or interviews, has a limitation on being applicable to children. This category does not apply to children unless the research involves educational tests or observations of public behavior, and the investigator does not participate in the activities being observed.
- **Category 3:** Research involving Benign Behavioral Interventions (BBI) through verbal, written responses, (including data entry or audiovisual recording) from **adult subject** who prospectively agrees.

In addition, there are two exempt categories that are NOT implemented at Children's Wisconsin:

- **CW does not utilize exemption categories 7 and 8.** These categories related to limited IRB review for the storage, maintenance, and secondary use of identifiable private information or identifiable biospecimens using **broad consent.** Because CW does not allow broad consent, these categories of exemption would not apply to any studies being conducted at CW.

Exempt Review categories

How a project moves through eBridge

When a project is submitted for review by the MCW pediatric IRB - the primary IRB used by CW for the function of IRB review - regardless of whether it will go to the convened board, be reviewed via the expedited pathway, or for an exempt determination. The eBridge system shows at what point in the process a study currently resides.

The workflow is as follows:

All submissions:

- It will first undergo normal Local Context Review procedures (see section 2.3.4 for details on LC review) by the CW HRPP Office to assess institutional concerns. The CW local context review is considered one of the ancillary reviews. If there are other ancillary reviews required, these will occur at the same time[A1] .
    - During this phase, the CW analysts will communicate via eBridge with the investigator/study team to address any institutional requirements or modifications to the submission required by the CW HRPP.
    - The submission will stay at this step in the review path until all ancillary reviews are complete.

- Once Local Context Review is complete (submission approved by the ancillary review) the study will undergo regulatory pre-review by the MCW HRPP office.
    - There will be communication with the investigator/study team by that office if anything needs to be addressed by the investigator.
    - The MCW HRPP and CW HRPP will discuss as needed any considerations in need of consistency in understanding between MCW and CW.

- Once IRB office review is complete:
    - **Convened board review path-** the submission will move to review by the MCW IRB's Full Board committee. The study will be assigned to a board meeting and the IRB committee and chair(s) will discuss the study, vote on whether to approve the study as written or request modifications, and make

other applicable determinations (such as pediatric risk level, assent requirements, waivers, etc.) Any motion requires a majority vote to pass.

- If the committee requires any modifications prior to approval, this will be communicated to the investigator via eBridge.
- Final approval letters, approved/stamped assent/parental permission/consent documents will be published in eBridge.

- **Expedited review -**the project is assigned to a delegated reviewer, rather than being assigned to an agenda for a convened meeting. That reviewer may communicate with the PI with questions.
  - An expedited reviewer can approve a project, or they may refer it to convened board if they deem this is appropriate. An expedited reviewer cannot disapprove a submission. If the reviewers have concerns about approvability it must go to the convened board for review.
  - If the reviewer requires any modifications prior to approval, this will be communicated to the investigator via eBridge.
  - Final approval letters, approved/stamped assent/parental permission/consent documents will be published in eBridge.

Approval Criteria for Full Board/Convened Board & Expedited research review

In order for the IRB to approve human subjects research through Full Board/Convened Board review or Expedited review, the following criteria must be satisfied for approval:

(1) Risks to subjects are minimized, and are reasonable in relation to any anticipated benefits (if any)

The goal of an IRB's risk assessment is to ensure that risks to research subjects posed by participation in the research are justified by anticipated benefits to the subject or society. As such, the IRB must determine:

- Whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit, justifies asking the potential subject to undergo any potential risks.
- Disapprove the research if risks are determined to be unreasonable in relation to anticipated benefits.

In order to assess risk/benefit of a proposed research study, the IRB will:

- **Identify the risks associated with the research**, as distinguished from the risks of activities that subjects would receive even if not participating in the research.

- **Determine whether the risks will be minimized** as much as possible by evaluating the necessity of proposed study procedures and their risks, and whether data for the study could be gained/retrieved from procedures already being performed for other purposes or alternative procedures that impart less risk than the proposed procedure.
- **Identify the anticipated benefits**, both direct and indirect, that participants, society, and/or science may gain from the research.
- **Determine whether the risks are reasonable in relation to the benefits**, and if there is any important knowledge to be gained from doing the research.

(2) Selection of subjects is equitable

When reviewing a proposed research study, the IRB will determine that the selection of subjects is equitable with respect to gender, age, class, race, ethnicity, socioeconomic status, etc. The IRB will not approve a study that does not provide an equitable selection of subjects, which includes an adequate ethical and scientific justification for excluding certain classes of potential subjects who might benefit from the research.

(3) Informed consent will be (a) sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extend required by the Federal Regulations (45 CFR 46.116), and (b) be appropriately documented, in accordance with, and to the extend required by the Federal Regulations (45 CFR 46.117)

The IRB will determine the need for informed consent, based on the research procedures.

(4) When appropriate, there are adequate provisions for monitoring the data collected to ensure the safety of subjects, and to protect the privacy of subjects and to maintain the confidentiality of data

When a study involves procedures that qualify as more than minimal risk to subjects, the IRB requires that the PI submit a data and safety monitoring plan with the proposed research study. This plan should adequately outline the procedures to be followed for safety monitoring, how the PI will ensure overview of the study risks, reporting of unanticipated problems involving risks to subjects or others, and descriptions of the interim safety reviews and procedures planned for reporting monitoring results to the IRB.

In reviewing a data and safety monitoring plan, the IRB will consider whether it is adequate for the research using the following guidelines:

- Monitoring is commensurate with the nature, complexity, size, and risk involved with the study.

- Monitoring is timely.
- Reporting of unanticipated problems or risks are promptly reported to the IRB in a timely manner.
- That the data and safety monitoring plan specifies (a) the entity or person(s) who will perform study monitoring, and the affiliation that entity or individual has with the sponsor/investigator, (b) the safety information that will be collected and monitored, such as serious adverse events and unanticipated problems, (c) the frequency of safety data review, (d) the procedures for analysis and interpretation of data, (e) procedures for scientific literature that may impact or inform safety or conduct of the study, (f) conditions that trigger suspension or termination of the research, and (g) procedures for IRB reporting.

Further, the IRB will evaluate whether the study team has an appropriate plan for protecting the privacy of subjects and maintaining the confidentiality of their data. In order to make this determination, the IRB must evaluate how the investigators plan to access, analyze, and store subjects' private, identifiable information. In making this determination, the IRB will consider:

- Methods used to identify and contact potential participants.
- Settings in which an individual will be interacting directly with the study team.
- Appropriateness of all individuals present for research activities.
- Methods used to obtain participant information, and the nature of information that is being requested/obtained from participants.
- Information being obtained about individuals that are not the "target subject" of the research, in order to determine if those individuals also meet the regulatory definition of "human subjects."

In addition, the IRB must determine that appropriate protections are in place to minimize the likelihood that this information will be inappropriately divulged outside of the scope of the research and determine that appropriate safeguards are commensurate with the potential of harm from unauthorized, inappropriate, or unintentional disclosure. When determining protections for subjects' confidentiality, the IRB will consider whether or not the collected/accessed data garnered for research purposes is sensitive, as well as the nature, probability, and magnitude of harms that could arise from a disclosure of this information outside of the research.

(5) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects

The IRB will determine whether certain individuals, by virtue of age or mental, physical, economic, educational, or other situation may be more vulnerable to coercion or undue influence to participate in a research study as compared to other populations. The IRB's review will determine whether inclusion of these vulnerable groups is appropriate based on scientific and ethical rationales, and will determine that, when applicable, additional safeguards are in place to protect those vulnerable subjects. For more information about vulnerable subjects, see here.