Children's Wisconsin
Kids deserve the best.

Tel: 414.337.7133
cwhrpp@childrenswi.org
See HRPP pages on Children's Connect

HRPP SOP Manual

Children's Wisconsin

Standard Operating Procedures
Human Research Protection Program

October 8, 2024

Please note: Some of the links throughout this document lead to information on the Children's Wisconsin Connect website. Because this is on the Children's Wisconsin network, to access you will need to be logged into the CW network via Citrix, or using a CW computer. From the initial landing page you can log into Connect using your CW credentials.

REVISED COMMON RULE INSERTED IN RED WITH COMMENTS

NOTE: This Children's Wisconsin ("CW") Human Research Protection Program ("HRPP") policy manual applies to research that is being overseen by an external IRB of record, or that has been submitted or transitioned to the MCW pediatric IRBs after July 1, 2022. For research that was previously overseen by the Children's Wisconsin IRBs, to access the archived Children's Wisconsin IRB policies and procedures for audit purposes, submit a request by email to the Children's Wisconsin HRPP: CWHRPP@childrenswi.org**.**

It is the expectation of the Children's Wisconsin HRPP that the IRB of record will follow Children's Wisconsin HRPP policies and will ensure consistency when making regulatory determinations as long as Children's Wisconsin HRPP policy does not conflict with applicable federal regulations.

Note: While MCW HRPP applies flexibility to some non-funded activities, CW does not extend that same flexibility to all CW research. Any acceptable flexibility for CW research will be described in this SOP manual and noted with ****FLX**.

Note: The CW HRPP will be part of the review of any research being conducted in CW space, with CW resources, or involving CW patients. Local regulations, institutional policies, and consent language will need to be considered and addressed for each local site. CW also will ensure that there are adequate resources to safely conduct the research and that all affected areas at CW agree to and can support the research. These issues need to be considered during the review process and are referred to as "**Local Context**". A local context review needs to

occur at the local site (CW) and information is then provided to the reviewing IRB. This includes verification that the site-specific information is incorporated appropriately in applicable study documents. It also is the process through which the local site verifies it has performed its relying site responsibilities as outlined in the reliance agreement. Local context review must be complete before final approval and before research can begin at CW. Local context review generally includes, but is not limited to, study-specific confirmation of:

- Application of local laws and institutional policies, requirements and expectations (as further defined in this SOP manual)
- Confirmation that all pre-submission requirements of CW are complete (for example if a pre-submission meeting with the PI is required)
- Training/qualifications of local investigators and research staff
- Ancillary reviews such as CW safety committee reviews and review by applicable CW departments
- Conflicts of interest disclosure review and management

Table of Contents

AAHRPP Accreditation Domains explanation

DOMAIN I: ORGANIZATION

In this Domain, the focus is on the obligations of the organization. This Domain describes the structural characteristics of the entity that assumes responsibility for the Human Research Protection Program (HRPP). The organization applies its HRPP to all research regardless of funding source, type of research, or place of conduct of the research. The organization exercises these responsibilities through relationships with researchers and research staff, IRBs, sponsors, participants, and the community.

The protection of research participants is the responsibility of many individuals involved with the HRPP, including IRB members, chairs, and staff; researchers and research staff; and the organizational official. The organization should define the roles and responsibilities of individuals responsible for the conduct or oversight of human research. Individuals should understand their roles and responsibilities.

An organization should communicate its expectations of those involved in research. Policies and procedures most relevant to researchers and research staff are different from those relevant to the IRB staff.

An organization should define all of the components (internal and external) that are involved with human research protection and ensure that those components communicate among themselves and function as an integrated program of protection.

External IRBs should consider not only components within their organization but also the components of organizations for which they serve as the IRB of record.

DOMAIN II: INSTITUTIONAL REVIEW BOARD

Within a Human Research Protection Program (HRPP), responsibilities must be delegated for providing ethical review and oversight of research. An organization may rely on one or more IRBs for review to supplement its resources. Relying on another IRB can facilitate research and increase the efficiency and cost-effectiveness of review.

An IRB is a body established generally under laws, regulations, codes, and guidance to protect the rights and welfare of human research participants and ensure the regulatory criteria for approval are met. The HRPP must have mechanisms in place to ensure the independence of the IRB review process and oversight functions, particularly with respect to decision-making regarding the ethics of research involving human participants. IRB structure, composition, operations, and review standards are set forth in laws, regulations, codes, and guidance.

DOMAIN III: RESEARCHER AND RESEARCH STAFF

The environment in which researchers and research staff conduct research and the type of research they conduct influence their roles and responsibilities. Competent, informed, conscientious, compassionate, and responsible researchers and research staff provide the best possible protection for human research participants. As part of its Human Research Protection Program, an organization can improve its protection of research participants if it has arrangements ascertaining and enhancing the competence of researchers and research staff.

1 Human Research Protection Program (AAHRPP Domain I)

Children's Wisconsin fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. In support of this, Children's Wisconsin has established a Human Research Protection Program (HRPP). The Children's Wisconsin HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under Children's Wisconsin auspices.

1.1 Mission

The mission of the HRPP is to:

- Safeguard and promote the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high-quality education, review, and oversight of human research projects; and
- To facilitate excellence in the conduct of human subjects research.

The HRPP includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants
- Exercise responsible oversight of human subjects research
- Assist in education of IRB members, investigators, and staff about their ethical responsibility to protect research participants in Children's Wisconsin space and about local site-specific considerations
- When appropriate, intervene in research and respond directly to concerns of research participants.

1.2 Organizational Authority

Children's Wisconsin Human Research Protection Program operates under the authority of the organization policy *Conduct of Research on Human Subjects at Children's Hospital and Health System*. That policy and the operating procedures in this document serve as the governing procedures for the conduct and review of all human research conducted under the auspices of CW. These HRPP policies and operating procedures are made available to all CW investigators and research staff and are posted on the Children's Wisconsin Administrative Policies & Procedures page and the CW HRPP website, both in Children's Connect.

1.3 Ethical Principles

Children's Wisconsin is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of transnational research, where consideration of alternative ethical principles may apply, Children's Wisconsin upholds and adheres to the principles of The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects in Research issued by the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. These principles are:

1. **Respect for Persons**, which involves the acknowledgment and support of autonomy, and protection of those with diminished autonomy
2. **Beneficence**, which involves ensuring that possible benefits of research are maximized, and possible harms are minimized
3. **Justice**, which involves the fair distribution of the benefits and burdens of research through the equitable selection of subjects

Children's Wisconsin HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under its auspices.

1.4 Regulatory Compliance

The HRPP facilitates compliance with federal regulations, state and local law and organizational policies (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe). Human subjects research at Children's Wisconsin is conducted in accordance with applicable regulations and requirements including, but not limited to, the following:

Human Subjects Research conducted, supported, or otherwise subject to regulation by any federal department or agency which adopts the Common Rule is reviewed and conducted in accordance with the Common Rule. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations (45 CFR 46).

Research subject to **FDA regulations** is reviewed and conducted in accordance with applicable regulations including, but not limited to, 21 CFR 50, 21 CFR 56, 21 CFR 312 and 21 CFR 812.

Research conducted or supported by the **Department of Justice (DOJ)** is subject to the **pre-2018 Common Rule** with regulations published at 28 CFR 46. The DOJ has established additional requirements for research conducted with the federal Bureau of Prisons (28 CFR 512) and research involving the National Institute of Justice (28 CFR 22). Investigators should consult these regulations and resources provided by NIJ when developing their research protocol. The IRB of record evaluates the research in accordance with these regulations when applicable. See the Special Topics section of this manual for more information.

When human subjects research is not subject to the Common Rule, FDA, or DoJ regulations, Children's Wisconsin ensures that human research subjects benefit from equivalent protections

by applying the Common Rule standards, with purposeful deviations that do not meaningfully diminish protections as noted within this manual. For example, while MCW HRPP applies flexibility to some non-funded activities, Children's Wisconsin does not extend all of the same flexibility to all Children's Wisconsin research. Any flexibility for Children's Wisconsin research will be described in this SOP manual (noted with **F) and will be assessed during Local Context review.

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the **Health Insurance Portability and Accountability Act** (HIPAA), 45 CFR Part 160, 162, and 164. See Section 27 of this manual for more information.

Several other U.S. federal departments and agencies have additional rules that apply to human subjects research that is supported by, conducted for or with, or involving the personnel or facilities of the department or agency. The IRB of record will evaluate such research in accordance with the applicable rules and requirements. Additional information regarding department/agency specific rules is available in the Special Topics section of this manual.

1.4.1 Management of pre-existing studies subject to the Common Rule

Refer to applicable **IRB** policies and procedures of the MCW pediatric IRBs or the IRB of record.

1.5 International Conference on Harmonization-Good Clinical Practice (ICH-GCP)

To facilitate the acceptance of data for regulatory review in participating countries, clinical trials subject to ICH-GCP should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and applicable regulatory requirements. Among other ICH-GCP guidelines, ICH-GCP E6 outlines guidelines for investigators, IRBs, sponsors, and others on how to do so.

When MCW commits investigators conducting research at Children's Wisconsin to comply with ICH-GCP E6 as a term of a grant or contract, investigators take on additional responsibilities. An investigator checklist is available on the CW HRPP website to support compliance with this requirement.

Reviewing IRBs may have their own SOPs regarding how they address and what their expectations are in relation to ICH-GCP E6. Investigators are responsible for familiarizing themselves with and following the reviewing IRB's requirements.

1.5.1 IRB Responsibilities

Refer to applicable **IRB** policies and procedures of the MCW pediatric IRBs or the IRB of record.

1.5.2 Investigator Responsibilities

In addition to the investigator responsibilities outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities;
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor;
3. The investigator should be aware of, and should comply with GCP and applicable regulatory requirements;
4. The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities;
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties;
6. The investigator must have adequate resources to conduct the trial, including:
    a. Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period;
    b. Sufficient time to properly conduct and complete the trial within the agreed trial period;
    c. Adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely; and
    d. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions;
7. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site;
8. If the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated;
9. A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions;
10. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware;

11. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and agrees to the primary physician being informed;
12. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights;
13. Before initiating a trial, the investigator must have written and dated approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects;
14. As part of the investigator's application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure (IB). If the IB is updated during the trial, the investigator should supply a copy of the updated IB to the IRB;
15. During the trial, the investigator should provide to the IRB all documents subject to review;
16. The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol;
17. The investigator may not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects;
18. In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor;
19. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol;
20. The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities for investigational product outlined in section 4.6 of ICH-GCP E6;
21. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding;
22. Additional requirements for Informed Consent -
    a. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive IRB's approval in advance of use. The subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented;

b. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's LAR;
c. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's LAR;
d. Neither the investigator, nor the trial staff, may coerce or unduly influence a subject to participate or to continue to participate in a trial;
e. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion;
f. Prior to participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects;
g. If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.
h. Consent for non-therapeutic trials (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) must be obtained from subjects who personally give consent and who sign and date the written informed consent form unless the IRB has expressly approved, in writing, that consent from a LAR is permitted;
i. The consent discussion and written informed consent form should include the following additional elements:
    i. An explanation of the trial treatment(s) and the probability for random assignment to each treatment;
    ii. An explanation of the subject's responsibilities (avoiding any language that appears to restrict subject's rights);

iii. An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access;
iv. An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial;
v. An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant;
vi. When there is no intended clinical benefit to the subject, the subject should be made aware of this;
vii. An explanation that, to the extent permitted by applicable laws or regulations, records identifying the subject will not be made publicly available, and, if the results of the trial are published, the subject's identity will remain confidential; and
viii. A statement that the trial has the approval of the IRB.

23. Investigators must comply with the requirements for records and reports outlined in section 4.9 and 8 of ICH-GCP E6;
24. Investigators must comply with the requirements for safety reporting outlined in Section 4.11 of ICH-GCP E6 including the redaction of personally identifying information; and
25. Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 of ICH-GCP E6 including the requirements for sponsor and IRB reporting.

1.6 Federalwide Assurance (FWA) and IRB Registration

The federal regulations require that federally-funded human subject research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an organization's assurance to the federal government that human subjects research conducted at that site complies with federal regulations pertaining to the protection of human subjects. Children's Wisconsin maintains a FWA on file with OHRP and ensures that it remains current.

When human subjects research is not subject to the Common Rule or FDA regulations, Children's Wisconsin ensures that human research subjects benefit from equivalent protections by applying the Common Rule standards, with purposeful deviations that do not meaningfully diminish protections as noted within this manual.

Likewise, federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations. Children's Wisconsin HRRP office maintains its FWA and IRB registration(s) in accordance with applicable regulations and guidance provided by OHRP and FDA.

CW relies primarily on the review services of the MCW pediatric IRBs. The HHS registration system database can be used to verify the status of Children's Wisconsin's FWA, IORG, and IRB of record registration.

Children's Wisconsin's Federal Registration Numbers	
FWA	FWA00001809
IORG	ORG0001622
IRB	IRB00013550 (MCW Pediatric IRB #7)
	IRB00013551 (MCW Pediatric IRB #8)

1.7 Research Under the Auspices of Children's Wisconsin

Research under the auspices of Children's Wisconsin includes research conducted at or using any property or facility of Children's Wisconsin, conducted by or under the direction of any employee or agent of Children's Wisconsin (including students) in connection with his or her Children's Wisconsin position or responsibilities, or involving the use of Children's Wisconsin's patients and/or non- public information (e.g., medical records) to identify, contact, or study human subjects. The research may be externally funded, funded from internal sources, or conducted without direct funding.

All human subjects research under the auspices of Children's Wisconsin is under the jurisdiction of the Children's Wisconsin HRPP. Human subjects research that Children's Wisconsin is engaged in (per OHRP or FDA guidelines) is under the jurisdiction of the Children's Wisconsin HRPP. The majority of research will have IRB oversight by the Medical College of Wisconsin (MCW) pediatric IRBs, unless Children's Wisconsin chooses to rely upon another IRB for review and ongoing IRB oversight of the research (the IRB of record for the research). The IRB agreement between MCW and Children's Wisconsin defines review by the Pediatric Specialty IRB committee (Board #7 or #8). In the event of studies being conducted in both a pediatric and adult population, the Dual Pediatric-Adult IRB committee (as defined by the IRB Agreement) must include appropriate pediatric specialists as required by the nature of the study, and if such committee is unable to satisfy this requirement the study shall be reviewed by the Pediatric Committee with appropriate pediatric specialty to provide input.

When external organizations and researchers wish to conduct research that is under the auspices of Children's Wisconsin, the external organization or researchers must consult with the Children's Wisconsin HRPP staff prior to initiating any research activities at or involving Children's Wisconsin.

1.8 Engagement in Research

Children's Wisconsin is responsible for ensuring appropriate oversight of the human subject research it engages in, including IRB approval of non-exempt human subject research.

OHRP defines engagement in guidance, stating:

> *"In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research."*

The guidance also states that institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for non-exempt human subjects research (i.e., awardee institutions), are also considered engaged in research even when all activities involving human subjects are carried out by employees or agents of another institution.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in Children's Wisconsin facilities or by Children's Wisconsin Principal or "Sub-Investigators" (as defined on the FDA 1572 or equivalent, or the delegation of responsibilities log) requires review by a Children's Wisconsin-designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when Children's Wisconsin involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

The HRPP Research Integrity Manager with the assistance and HRPP staff, and legal counsel as needed, are authorized to determine whether Children's Wisconsin is engaged in a particular research study. Investigators and other institutions **may not** independently determine whether Children's Wisconsin is engaged in a particular research study.

When Children's Wisconsin is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB.

For additional information on engagement please refer to OHRP's Guidance on Engagement on Institutions in Human Subjects Research.

1.9 Key Definitions

Human Subjects Research. Human Subjects Research means any activity that meets the definition of "research" and involves "human subjects" as defined by the Common Rule or other applicable regulations (e.g., FDA).

Note: The terms "subject" and "participant" are used interchangeably in this document and have the same definition.

Minimal Risk. 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.

Common Rule. The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the

purposes of this document, references to the Common Rule will cite the DHHS regulations. The Common Rule was updated in 2018, throughout this manual references to the "pre-2018 Common Rule" (or requirements) apply to studies approved or determined exempt prior to January 21, 2019 that have not been transitioned to comply with the 2018 Common Rule. References to the "2018 Common Rule" (or requirements) or the "revised Common Rule" apply to studies approved or determined exempt on or after January 21, 2019.

Pre-2018 Common Rule Definitions:

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

For the purposes of these policies and procedures, a **"systematic investigation"** is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

Human subject. Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention. Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction. Interaction includes communication or interpersonal contact between investigator and subject. *Please note that per OHRP interaction includes indirect means of communication such as via completion of a web-based survey.*

Private Information. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Identifiable. Identifiable information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

2018 Common Rule Definitions:

Clinical Trial. Per the 2018 Common Rule and NIH Policy, clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. FDA regulations refer to "clinical investigations" (see definition of "research" below).

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. [45 CFR 46.102(e)(1)]

Intervention means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(e)(2)]

Interaction means communication or interpersonal contact between investigator and subject. *Please note that per OHRP interaction includes indirect means of communication such as via completion of a web-based survey.*

Private information means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Identifiable private information means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. [45 CFR 46.102(e)(5)]. *Note: This definition is within the 2018 Common Rule. For a discussion of identifiability under HIPAA, please see* ***Privacy- Uses and Disclosures of Protected Health Information (PHI) for Research Purposes***.

Identifiable biospecimen means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen [45 CFR 46.102(e)(6)]

Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the

nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

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.

Public health authority means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

> For purposes of this part [the Common Rule], the following activities are deemed not to be research: (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected. (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority*. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters). (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes. (4) Authorized operational activities (as determined by

each agency) in support of intelligence, homeland security, defense, or other national security missions. [45 CFR 46.102(l)]

*NIH issues determinations about whether NIH-supported or conducted activities qualify as public health surveillance activities deemed to be "not research" under the revised Common Rule. Investigators and institutions may not make their own determinations.

For the purposes of these policies and procedures, a **"systematic investigation"** is an activity that involves a study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings. In accordance with OHRP guidance, the establishment of a research repository is also considered a systematic investigation intended to develop generalizable knowledge.

Food & Drug Administration (FDA) Definitions:

Research. The FDA has defined "**research**" as being synonymous with the term "**clinical investigation**." A clinical investigation, as defined by FDA regulations, means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Human Subject. Human subject means an individual who is or becomes a participant in a clinical investigation, either as a recipient of the test article or as a control. A subject might be either a healthy individual or a patient. For research involving medical devices

a human subject is also an individual on whose specimen an investigational device is used or tested or used as a control (regardless of whether the specimens are identifiable). [21 CFR 50.3(g), 21 CFR 312.3(b), 21 CFR 812.3(p)]

Test Article. Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [21 CFR 50.3(j)]

Test articles covered under the FDA regulations include, but are not limited to:

1. **Human drugs** – A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process). The primary intended use of a drug product is achieved through chemical action or by being metabolized by the body.
2. **Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term “device” does not include software functions excluded pursuant to section 520(o)."

   The 21st Century Cures Act amended the FD&C Act to specifically exclude certain software functions from the definition of medical device. Summarized, these include exclusions for software functions intended for administrative support of a health care facility; for maintaining or encouraging a healthy lifestyle; to serve as electronic patient records; for transferring, storing, converting formats, or displaying clinical laboratory tests or other device data and results and related information; and for displaying, analyzing, or printing medical information, for supporting or providing recommendations to a health care professional, and enabling the health care professional to independently review the basis for such recommendations. Additional information regarding the application of these exclusions is available on FDA’s “Guidances with Digital Health Content” website.

3. **Human Cells, Tissues, or Cellular or Tissue-based Products** (HCT/P's) – HCT/P's means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

   The following articles are not considered HCT/P's: vascularized human organs for transplantation; whole blood or blood components or blood derivative products subject to listing under parts 607 and 207, respectively; secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P; minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); ancillary products used in the manufacture of HCT/P; cells, tissues, and organs derived from animals other than humans; in vitro diagnostic products as defined in 809.3(a); blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

4. **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.

5. **Dietary Supplements** – A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of drug, it is regulated as such.

6. **Medical Foods** – A medical food, as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)), is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

7. **Mobile Medical Apps** - Mobile apps are software applications that can be executed on a mobile platform or a web-based software application that is tailored to a mobile platform but is executed on a server. Mobile medical apps are a subset of mobile apps that medical devices that meet the definition of a medical device and either are intended to be used as an accessory to a regulated medical device; or to transform a mobile platform into a regulated medical device.
8. **Radioactive Drugs** – The term radioactive drug means any substance defined as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes "radioactive biological product".
9. **Radiation-Emitting Electronic Products** - a radiation-emitting electronic product as any electrically-powered product that can emit any form of radiation on the electromagnetic spectrum. These include a variety of medical and non-medical products such as mammography devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).

1.10 Written Procedures

These Standard Operating Procedures (SOPs) for Human Research Protection detail the procedures, standards, and requirements for research with human subjects under the auspices of Children's Wisconsin. This is not a static document. The SOPs are reviewed at a minimum of annually and revised by the Research Integrity Manager (or designee) in consultation with the Institutional Official. The Institutional Official will approve all revisions of the SOPs.

The Children's Wisconsin HRPP will keep the research community apprised of new information that may affect the human research protection program, including laws, regulations, policies, procedures, and emerging ethical and scientific issues on its website, through email, and other forums. These SOPs will be available on the Children's Wisconsin HRPP website and Children's Connect policy page. Changes to the SOPs are communicated to investigators and research staff by way of the regularly published HRPP newsletter.

1.11 Children's Wisconsin HRPP Structure (referred to "descriptions of components")

The HRPP consists of individuals, departments, and committees with responsibilities for human research protections such as the Institutional Official, Research Integrity Manager, Corporate Compliance, Pediatric Translation Research Unit, Research Pharmacy, Legal Counsel, HRPP staff, investigators, research staff, the Radiation Safety Committee (RSC), the MRI safety committee,

the MCW Institutional Biosafety Committee (IBC), the Research Conflict of Interest Committee, and others. The objective of this system is to assist the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

The following officials, administrative units and individuals have primary responsibilities for human subject protections:

1.11.1 Institutional Official

The ultimate responsibility of the HRPP resides with the Institutional Official (IO) of the program. The IO is legally authorized to represent Children's Wisconsin. The IO is the signatory of the FWA and assumes the obligations of the FWA. At Children's Wisconsin the Vice President Research Administration is the Institutional Official. The IO is responsible for ensuring that the Children's Wisconsin HRPP and IRB(s) have the resources and support necessary to fulfill their responsibilities and to comply with the regulations and requirements that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program;
- Appropriate office space, meeting space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of noncompliance;
- Access to legal counsel; and
- Ensuring that the investigators and staff receive training related to human research protections.

At a minimum of annually, the IO reviews HRPP and IRB functions, requirements, and resources and makes adjustments as needed.

The IO is also responsible for:

- Fostering, supporting and maintaining a culture that supports the ethical conduct of research involving human subjects and compliance with applicable regulatory and other requirements;
- Ensuring that the MCW pediatric IRBs and Children's Wisconsin HRPP function independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function or independence of the reviewing IRBs;
- Oversight of the Institutional Review Boards (IRBs) Children's Wisconsin relies upon;
- Oversight over the conduct of human subjects research under the auspices of Children's Wisconsin

- Providing training and educational opportunities for IRB members and HRPP staff to support their ability to review research in accordance with ethical standards, applicable regulations and Children's Wisconsin expectations;
- Providing training and educational opportunities for investigators and research staff to support their ability to conduct research in accordance with ethical standards and applicable regulations; and
- Taking action as necessary to ensure the protection of human subjects and compliance with regulatory and other requirements.

The IO has the authority to suspend, terminate, or disapprove research or take other actions, such as sanctions or restrictions of research privileges or uses of research data, as necessary, to ensure the proper conduct of research, the protection of human subjects, the autonomy and authority of the IRBs of record, compliance with regulatory and other requirements, or to protect the interests of Children's Wisconsin. However, the IO may not approve research that has been disapproved (or not yet approved) by the IRB of record.

The IO must complete the OHRP Human Subject Assurance Training. The HRPP Office will support the continuing education of the IO by providing information and updates on topics related to human research protections.

The IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The Research Integrity Manager and reviewing IRB Chairs have access to the IO for any concerns or issues related to the HRPP or IRB of record.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about human subject protections and research at the organization.

1.11.2 Research Integrity Manager

The Research Integrity Manager (RIM) is selected by and reports to the Institutional Official (IO) and is responsible for:

- Developing, managing and evaluating policies and procedures that ensure compliance with state and federal regulations and Children's Wisconsin policies. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the HRPP;
- Advising the IO on key matters regarding human subjects research;
- Implementing the organization's HRPP SOPs;
- Overseeing the administration of the HRPP, including the supervision of staff;
- Overseeing the administration of IRB Reliance Agreements and Independent Investigator Agreements;

- Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP);
- In consultation with the IO, evaluating the financial resources of the Children's Wisconsin HRPP;
- Assisting the IRBs of record in its efforts to review research and ensure the protection of human subjects;
- Assisting investigators in their efforts to carry out the organization's research mission;
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;
- Developing training requirements as required and as appropriate;
- Serving as the primary contact at Children's Wisconsin for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA), and other regulatory agencies on matters of human research protections; and
- Serving as an internal expert resource for questions and other matters regarding the protection of human subjects.

1.11.3 HRPP Staff

In addition to the leadership structure described above, staffing for the HRPP must remain sufficient to support the activities of the HRPP. The HRPP staff for Children's Wisconsin must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The Children's Wisconsin HRPP staff report to the Research Integrity Manager who has day-to-day responsibilities for its operations.

1.11.4 Institutional Review Board (IRB)

Children's Wisconsin relies on external IRBs as appointed by the Institutional Official (IO), including the MCW pediatric IRBs (as defined by the Institutional Review Board Services Agreement between MCW and Children's Wisconsin). These external IRBs prospectively review and make decisions concerning all non-exempt human subjects research under the auspices of Children's Wisconsin unless it has been determined that Children's Wisconsin is not engaged in the research. In addition to the HRPP, the IRBs are responsible for the protection of the rights and welfare of human research subjects, through review and oversight of safe and ethical research. They discharge this duty by complying with the requirements of federal and state regulations, the FWA, and CW HRPP and organizational policies.

The IRBs of record function independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes independent determinations whether to approve, require modification in, or disapprove research based upon whether human subjects are adequately protected.

Research that has been reviewed and approved by the IRB of record may be subject to review and disapproval by officials of the organization. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

1.11.5 Legal Counsel

The Children's Wisconsin HRPP relies on the Organization's Legal Counsel or designee for the interpretation of state law and the laws of other jurisdictions where research is conducted as they apply to human subject research. Counsel is available to provide guidance on other relevant topics as needed.

1.11.6 Department Chairs and/or Organizational Leaders

The IRB is not able to begin their review of a submission until the designated departmental reviewer indicates approval on behalf of their department and/or division. Department chairs and/or administrative leaders are required to review and sign all new study proposals submitted to the IRB for review. This will be indicated by a sign off on the project in an electronic submission system by Department Chairs and/or the appropriate Children's Wisconsin administrative leaders (see Essential Contacts list). Sign off can be done via one of the following methods and included with the submission to the IRB:

- Including a signed memo in the submission indicating approval of the project
- Including an email from the appropriate department chair and/or CW administrative leader indicating the project has undergone departmental/administrative review may be submitted for IRB review.

This sign off is an attestation by the Department Chair that the proposal has undergone a departmental review process that includes assurance that:

- The Principal Investigator is a faculty member, credentialed physician, nurse scientist, pharmacist, Versiti or Children's Wisconsin employee (as applicable) in good standing;
- The Principal Investigator is approved to devote the proposed time and effort to this project;
- If the Principal Investigator's application identifies Department/Division/Institute funds to support this project, this Department/Division/Institute endorses this commitment;
- The project has scientific merit, uses procedures consistent with sound research design, and is likely to yield the expected knowledge; and
- The proposal is a complete and coherent one.

This administrative sign off is an attestation by the CW administrative leader of the CW area that will be affected by the research that:

- It is acceptable for the department/unit's resources be utilized to conduct the research
- It is agreeable to any potential disruption in day to day operations due to the research activities being conducted in that area

- There is appropriate private space available if the informed consent process would be taking place in the department/unit

1.11.7 Principal Investigators

The Principal Investigator (PI) is ultimately responsible for the protection of the human subjects participating in research they conduct or oversee. The PI is expected to abide by the highest ethical standards when developing a research plan and to incorporate the principles of the Belmont Report. The PI is expected to conduct research in accordance with the IRB approved research plan and to personally conduct or oversee all aspects of the research.

In addition to complying with all applicable regulatory policies and standards, PIs must comply with organizational and administrative requirements for conducting research. The PI is responsible for ensuring that all investigators and research staff complete all organization required trainings as well as training for their specific responsibilities in any given research study. When investigational drugs or devices are used, the PI is responsible for ensuring an appropriate plan for their storage, security, dispensing, accounting, and disposal.

The HRPP reviews investigator qualifications when reviewing research and may determine that an investigator may not serve as PI or may require the addition of other investigators to supplement the expertise available on the research team or to conduct or oversee certain aspects of the research.

Please refer to the CW policy Research: Conduct of Research on Human Subjects at Children's Hospital and Health Systems for more information, including who can serve as PI. Individuals who are debarred, disqualified, or otherwise restricted from participation in research or as a recipient of grant funds for research by a federal, state, or other agency may not serve as PI.

Individuals with a history of compliance issues related to the conduct of research (e.g., recipients of an FDA Warning Letter) will be considered on a case-by-case basis. Factors to consider include whether corrective actions have been accepted as adequate, whether information from an audit or quality review indicates that the issues have been resolved, and similar considerations.

1.11.8 Other Related Units

1.11.8.1 Children's Wisconsin Pharmacy

A pharmacist from Children's Wisconsin Hospital Pharmacy serves as the investigational drug pharmacist on the MCW pediatric IRB. In addition, the designated pharmacist has access to the electronic submission system, allowing the Pharmacy to have complete information about all IRB approved research that takes place at Children's Wisconsin and under its jurisdiction. The designated pharmacist assures that information about all studies involving drugs used in research is shared with both the Pharmacy Staff as appropriate and that the Children's Wisconsin Hospital Pharmacy and Therapeutics Committee is made aware of all studies approved by the IRB of record for research involving drugs. The designated pharmacist is

required to sign off on any studies that involve an investigational drug, and sign off is verified during local context review.

Children's Wisconsin Pharmacy is responsible for storing, accounting for, dispensing, and compounding of most investigational drugs used in research, whether conducted inpatient or outpatients. The manufacture/compounding of drug products not commercially available is coordinated by Children's Wisconsin pharmacy. Waivers from use of the Children's Wisconsin pharmacy for handling investigational drugs will be considered on a case by case basis by both the IRB and the Children's Wisconsin pharmacy, with required information regarding storage, accounting, dispensing etc. provided within the IRB application.

The Pharmacy is available to provide guidance to investigators in relation to the management of the study drugs.

1.11.9 Purpose of the Children's Wisconsin HRPP Leadership Committee

The Children's Wisconsin IRB Chairs Committee will meet as needed periodically to ensure a dialogue is maintained between the various individuals and offices with responsibilities for research compliance at Children's Wisconsin. Membership is comprised of:

- Chairs of MCW pediatric IRB committees
- Pediatric Associate Director
- CW Institutional Official
- CW Research Integrity Manager

This committee will act in an advisory capacity monitoring the effectiveness of existing programs, discussing new or revised policies as changes in requirements occur, and disseminating updates to the research community.

1.11.10 Study-Specific Coordination

In addition to IRB approval, PIs must obtain and document the approval, support, or permission of other individuals and departments or entities impacted by the research as well as approval by other oversight committees, including, but not limited to:

- Pathology/laboratory
- Pediatric TRU
- Primary Care - Director Quality and Patient Safety – Primary Care
- Pharmacy
- Radiology
- Nursing
- Facilities where research activities will occur (CW administrator overseeing the CW unit/clinic/etc.)
- Departmental approvals
- Records access permissions (e.g., Medical/Educational Records)

- Institutional Biosafety Committee
- Radiation Safety Committee
- MRI Safety Committee
- Research Conflict of Interest Committee
- Scientific/Scholarly Review Committee (if available in the department conducting the research)

When applicable, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Study Application to the IRB of record. Alternatively, sign-off in the electronic submission system by the individual granting the approval is acceptable. The application will be reviewed by the HRPP office during local context review to ensure that all necessary letters are included. The IRB may request review by or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not required by policy. Final approval will not be granted until all required approvals are obtained and submitted.

If the study is modified after initial approval such that new or additional approvals would be required, those approvals must be included with the amendment submission.

If the research sites, or research personnel, are also under the jurisdiction of another IRB, documentation of the external IRB's approval or agreement to cede or waive review is required.

Other committees and officials may not approve research involving human subjects to commence that has not been approved or has been disapproved by the IRB of record.

2 Quality Assurance (AAHRPP Domain I)

Children's Wisconsin HRPP office performs Quality Assurance and Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws. In addition, Children's Wisconsin Corporate Compliance will conduct compliance audits according to their audit plan.

2.1 External Monitoring, Audit, and Inspection Reports

The CW HRPP and department Chairs, Research Compliance, Investigational Pharmacy, if applicable, should be notified in advance, whenever possible, of upcoming audits or inspections of research reviewed by an external IRB on Children's Wisconsin's behalf. HRPP representatives may participate in entrance and exit interviews and otherwise observe or support the audit or inspection. Likewise, Children's Wisconsin representatives may assist in the development of any responses to audits or inspections.

When Children's Wisconsin is engaged in research reviewed by an external IRB (including MCW pediatric IRBs), all reports from audits or inspections must be submitted to the HRPP for review via a reportable event in the electronic submission system. The HRPP may require corrective

and preventative actions (CAPA), a follow up review, or other actions as needed to ensure the protection of human subjects and to support compliance.

Reports indicative of any negative actions by a government oversight office regarding research conducted at or by Children's Wisconsin must be immediately reported to the CW HRPP office by phone or email. These actions include, but are not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections.

2.2 Investigator Compliance Reviews (aka Post-Approval Monitoring)

Children's Wisconsin Corporate Compliance will conduct compliance audits according to their audit plan. The HRPP Quality and Operations Specialist with assistance of other internal or external staff, will conduct post-approval directed and routine reviews ("Reviews") of human subjects research conducted under the auspices of Children's Wisconsin.

HRPP Reviews are conducted to assess investigator compliance with federal, state, and local law, and Children's Wisconsin policies, and to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of Reviews will be reported to the Research Integrity Manager, the investigator, the Institutional Official (IO) and other Children's Wisconsin leadership, Corporate Compliance, as appropriate. Any IRB reporting and evaluation of noncompliance will be handled according to the procedures of the IRB of record for the study reviewed.

If it is identified during the course of a review that subjects in a research project may have been exposed to unexpected serious harm or risk of harm, the reviewer will promptly report such findings to the HRPP Research Integrity Manager and the IRB of record.

If issues are identified that indicate possible misconduct in research, the procedures of the appropriate organization's Research Misconduct and/or Non-Compliance policy may be initiated by Corporate Compliance. HRPP Reviews may include:

- Requesting progress reports from investigators
- Examining investigator-held research records and records held by pharmacy or other ancillary services
- Reviewing source documentation
- Reviewing the recruitment process and materials
- Reviewing consent materials and the documentation of consent
- Observing the consent process and other research activities
- Interviewing investigators and research staff
- Interviewing research subjects
- Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review

- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP, IO, or IRB of record

2.3 IRB Compliance Reviews

The Children's Wisconsin Research Integrity Manager and/or the CW HRPP staff, will periodically review the activities of the IRBs of record to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of IRB records.

Review activities may include:

- Review of the IRB minutes to evaluate whether adequate documentation of the meeting discussion and any required determinations has occurred, and that quorum was met and maintained
- Reviewing IRB files to evaluate whether adequate documentation of exemptions, expedited review, and other outside of committee reviews has occurred
- Reviewing consent forms to evaluate whether all required elements are included
- Reviewing the IRB databases to evaluate whether all required fields are completed accurately
- Reviewing metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process
- Committee composition of the MCW Pediatric IRBs (as defined by the Institutional Review Board Services Agreement executed July 1, 2021 and if amended)
- Performance metrics for MCW Pediatric IRBs turnaround times (as defined by the Institutional Review Board Services Agreement executed July 1, 2021 and if amended)
- Other review activities as appropriate

The Research Integrity Manager, in consultation with the IRB of record (including appropriate IRB administrators), will review the results of IRB compliance reviews with the IO. If substantive deficiencies are identified in the review, a corrective action plan will be approved by the Research Integrity Manager and IO. The IRB of record will have an opportunity for implementing and reporting progress on the corrective action plan, the results of which will be evaluated by the Children's Wisconsin IO.

2.4 HRPP Quality Assessment and Improvement

Annually, a meeting is held by the Research Integrity Manager and the HRPP Quality & Operations Specialist to establish a quality assessment/ improvement (QA/QI) plan to assess the compliance, and the quality, efficiency, and effectiveness, of the HRPP. The plan will include, at a minimum, the following:

- The goals of the plan with respect to achieving and maintaining compliance
    - At least one objective to achieve or maintain compliance
    - At least one measure of compliance

- The methods to assess compliance and make improvements

- The goals of the plan with respect to achieving targeted levels of quality, efficiency, and effectiveness
  - At least one objective of quality, efficiency, or effectiveness
  - At least one measure of quality, efficiency, or effectiveness
  - The methods to assess quality, efficiency, or effectiveness and make improvements.

The Research Integrity Manager will meet regularly throughout the year with the staff responsible for performing the assessments called for in the plan to review progress and to identify opportunities for improvement. At the end of each year, the Research Integrity Manager, and other parties as appropriate, will evaluate whether the respective goals were achieved and determine if any additional actions or monitoring are necessary. If at any time substantive or concerning issues or trends are identified, the Research Integrity Manager will report those issues or trends to the appropriate parties (e.g., the IO, the IRB of record Chairs, Research Compliance) and, if appropriate, a proposed CAPA plan.

In addition to the above, the Research Integrity Manager or designee are responsible for tracking internal data and metrics that are informative when considering HRPP efficiency, effectiveness, workload, and resources. Metrics reports will be provided to the IO on a regular basis.

3 Education & Training (AAHRPP Domain I)

3.1 Training / Ongoing Education HRPP Staff

Recognizing that a vital component of a comprehensive human research protection program is an education program, Children's Wisconsin is committed to providing training and on-going education related to ethical concerns and regulatory and organizational requirements for the protection of human subjects specific to Children's Wisconsin considerations.

Initial Education

HRPP staff must complete the required modules in the CITI Course in the Protection of Human Research Subjects (IRB member, biomedical, or social behavioral), or other training determined to be equivalent by the Research Integrity Manager. HRPP staff onboarding process is described as part of department-specific new employee orientation.

In addition to CITI training, Children's Wisconsin also uses the following activities as a means for offering continuing education to HRPP staff:

- In-service training at HRPP staff meetings
- Training workshops

- Webinars
- Email distribution of articles, announcements, presentations, and other materials relevant to human subject protections

HRPP staff are also required to complete CITI basic or refresher training every 3 years or other training determined to be equivalent by the Research Integrity Manager.

The activities for continuing education vary on a yearly basis depending on areas of need, as determined by the Research Integrity Manager and HRPP Quality & Operations Specialist. Whenever possible, the HRPP provides support for staff to attend PRIM&R, OHRP, AAHRPP or other relevant conferences.

3.2 Training / Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive human research protection program is an education program for all individuals with human subject responsibilities. Children's Wisconsin is committed to providing training and on-going education for investigators and research staff members on human subject protections and other relevant topics.

3.2.1 Initial Education

Investigators and research staff who interact or intervene with subjects, or who use subject's identifiable information for the purposes of research, must complete CITI Courses relevant to the type of research being conducted and the investigator or staff member's responsibilities. Children's Wisconsin partners with the Medical College of Wisconsin in creating and assigning CITI courses which are used by both MCW and CW. A guidance titled Human Subjects Research Protections Training Requirements detailing Children's Wisconsin CITI training requirements is available on Children's Wisconsin HRPP web pages. Circumstances under which Children's Wisconsin may accept human subject research protections training from another institution are described in this guidance in the section *CITI Training Requirements – Study Staff from Other Institutions*.

Evidence of current training (date of completion within 3 years of application date) for each member of the research team must be available for review with every new study application and applications to add study personnel. New study applications and additions of study personnel will not be moved forward for IRB review without evidence of training.

3.2.2 Continuing Education

Initial training is considered current for a period of 3 years by which time investigators and research staff must complete basic or refresher CITI training or provide evidence of equivalent training as described above. There is no exception to this requirement.

Training will be verified at the time of initial submission, continuing review or research status report and with applications to add study personnel. If training has not been completed or has lapsed and is not completed in a timely manner, the investigator or staff member may be removed from the study or otherwise restricted from participating in the research.

In addition to the basic requirements described above, Children's Wisconsin will periodically provide training on topics relevant to human subject protections, regulations, policies and standards, and IRB submission processes and requirements. Training may be provided via in-service, workshops, webinars, e-Learning, or through the distribution of articles, presentations, and other materials.

Investigators and staff may request training or offer training suggestions by contacting the HRPP Quality & Operations Specialist or the Research Integrity Manager.

4 "Research" and "Human Subjects Research" Determinations (AAHRPP Domain I)

The responsibility for initial determination whether an activity constitutes "research" rests with the individual with primary responsibility for the activity. This individual should make this determination based on the definitions of "research" and "clinical investigation" as provided by the Common Rule and FDA regulations, respectively (See definitions in Section 1.9). Consultation with the HRPP Office is encouraged. More information can be found in the guidance document Guidance: Human Subjects Research Determinations.

Because the analysis can be complex, individuals with any questions regarding the applicability of the regulations to their activities at Children's Wisconsin are urged to request a determination that an activity does or does not involve research. Such requests should be submitted using the form Request for Determination of Human Subject Research (HSR) which can be found on the HRPP website. This form should be submitted following detailed submission instructions in this form

Similarly, the responsibility for the initial determination of whether research involves "human subjects" rests with the investigator. Under the Common Rule, information is considered identifiable, and thus involving human subjects, when the identity of the subject is or may readily be ascertained by the investigator or associated with the information. It should be noted that this definition differs significantly from de-identified in accordance with HIPAA standards. FDA regulations do not incorporate the concept of "identifiability" in the evaluation of whether an activity is a clinical investigation (or research) subject to FDA regulations. For example, the use of de-identified human specimens to evaluate the safety or effectiveness of a diagnostic device is considered human subjects research subject to FDA regulations. Investigators are urged to submit for a determination whenever they are uncertain if a research study involves "human subjects" as defined by the Common Rule or FDA. Investigators are urged to submit for a determination whenever they are uncertain if a research study conducted at Children's Wisconsin involves "human subjects" as defined by the Common Rule or FDA.

Such requests should be submitted using the form Request for Determination of Human Subject Research (HSR).

Investigators **may not** self-determine that research involving the use of **coded** private information or specimens does not involve "human subjects". Such determinations may only be made by the HRPP using the process described above. The only exception to this policy is when the research is not subject to FDA regulations and the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the key or code that would enable re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

Human Subjects Research Determinations must be submitted, and determined, prospectively (i.e., before the proposed activity or research begins). Conducting human subjects research without IRB approval or exemption is noncompliance and will be managed as described in Section 18.

Determinations whether an activity constitutes human subject research will be made by the Research Integrity Manager (or designee) and/or MCW pediatric IRB Chair according to the definitions in Section 1.9, applicable federal regulations, and federal guidance. A written determination will be sent via email with the completed determination form attached. Investigators conducting research under the auspices of Children's Wisconsin may not rely upon determinations made by other organizations or through the use of electronic (or other) determination tools.

Note: With the implementation of the revised Common Rule, the requirement of the Newborn Screening Saves Lives Reauthorization Act of 2014 that federally funded "research on newborn dried blood spots shall be considered research carried out on human subjects" is eliminated. Whether such research involves human subjects shall now be considered using the same standards as are used for other research involving human biospecimens (e.g., whether the identity of subjects may be readily ascertained, whether the specimens are coded and who has access to the key, whether the research involves the evaluation of the safety or effectiveness of an FDA-regulated device, etc.).

5 Exempt Determinations (AAHRPP Domain I)

All research involving human subjects must be reviewed by a Children's Wisconsin designated IRB for the determination. Children's Wisconsin may also choose to accept an exempt determination made by an external IRB. Children's Wisconsin HRPP will consider such requests on a case-by-case basis.

Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers must not have any apparent conflict of interest.

Unless otherwise required by law or by Federal department or agency heads, exempt studies are exempt from the requirements of the Common Rule (i.e., IRB approval and full research

consent are not required) other than as specified within the regulations (e.g., the conditions that permit exemption, and when limited IRB review is required). Exempt research is not exempt from ethical considerations, such as honoring the principles described in the Belmont Report. The individual(s) making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

5.1 Limitations on Exemptions

The following limitations on exemptions apply to research conducted at Children's Wisconsin:

For research subject to the pre-2018 requirements, including research subject to DOJ regulations:

Children: The exemption for research involving survey or interview procedures or observations of public behavior (#2) does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.

Prisoners: Exemptions do NOT apply. IRB review is required.

For research subject to the revised Common Rule (2018 requirements):

> **Children:** Exemption #2(i) and (ii) for research involving survey or interview procedures or observations of public behavior does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed. Exemption #2(iii), where identifiable information is obtained and the IRB conducts a limited IRB review, is NOT applicable to research in children. Exemption #3 does NOT apply to research involving children. [45 CFR 46.104(b)(3)]
>
> **Prisoners:** Exemptions do not apply except for research aimed at involving a broader subject population that only incidentally includes prisoners. [45 CFR 46.104(b)(2)]

5.2 Categories of Exempt Research

With the above-referenced limitations and any other limitations or restrictions due to applicable law, regulation, or agency policy, research activities not regulated by the FDA (see section below for FDA Exemptions) in which the only involvement of human subjects is determined to be in one or more of the following categories may be determined exempt:

For research subject to the pre-2018 Common Rule requirements, including research subject to DOJ regulations:

1. Pre-2018 Exemption Category 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as

   (i) research on regular and special education instructional strategies, or

(ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Pre-2018 Exemption Category 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

   (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

   (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.

3. Pre-2018 Exemption Category 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under pre-2018 exemption category 2, if:

   (i) the human subjects are elected or appointed public officials or candidates for public office; or

   (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Pre-2018 Exemption Category 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

NOTE: To be eligible for this exemption, all of the materials have to already be in existence at the time the research is proposed for an exempt determination.

5. Pre-2018 Exemption Category 5: Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:

   (i) Public benefit or service programs;

   (ii) Procedures for obtaining benefits or services under those programs;

   (iii) Possible changes in or alternatives to those programs or procedures; or

   (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).

The research demonstration project must be conducted pursuant to specific federal statutory authority, there must be no statutory requirements of IRB review, the research must not involve significant physical invasions or intrusions upon the privacy of subjects, and the exemption must be invoked only with authorization or concurrence by the federal funding agency.

6. Pre-2018 Exemption Category 6: Taste and food quality evaluation and consumer acceptance studies,

   (i) If wholesome foods without additives are consumed; or

   (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

For research subject to the revised Common Rule (2018 requirements):

1. Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

   i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through

identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

    A. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    B. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

    (ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

    (iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

i. The identifiable private information or identifiable biospecimens are publicly available;
ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.
   i. Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal website or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or

demonstration project must be published on this list prior to commencing the research involving human subjects.

6. Taste and food quality evaluation and consumer acceptance studies:

    i. If wholesome foods without additives are consumed, or
    ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

5.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB review and approval:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [21 CFR 56.104(c)]

   See Section 16.10 for detailed discussion of this exemption.

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR 56.104(d)]

5.4 Procedures for Exemption Determination

To request an exempt determination, investigators should following the MCW IRB submission process.

Note: Current CITI training for all members of the research team is required as per CW policy and will be verified during CW LC review.

The designated reviewer will follow the MCW IRB exempt submission review process for the review and documentation of the determination. If the request does not appear to meet the definition of human subject research, the reviewer withdraws the request and notifies the requestor that a *Request for Determination of Human Subject Research (HSR)* form should be submitted.

The individual reviewer making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

A letter documenting the outcome of the review will be published in the IRB electronic system. The exempt application, review documentation, and determination letter are maintained in the same manner and for the same length of time as other IRB review documentation.

6 IRB Reliance (AAHRPP Domain I)

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, Children's Wisconsin acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. Children's Wisconsin will rely on the review of another qualified IRB. When Children's Wisconsin is the prime awardee on an HHS grant, it will ensure that at least one IRB reviews the research in its entirety.

When relying upon another IRB, a formal relationship must be established between Children's Wisconsin and the outside organization or investigator through an IRB Authorization Agreement, Investigator Agreement, a Memorandum of Understanding, or other such written reliance agreement. The written agreement must be executed before Children's Wisconsin will accept any human research proposals from the outside organization or investigator or rely on the review of an external IRB.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information-sharing, and reports, may be outlined in the reliance agreement, in SOPs, or other written materials. Children's Wisconsin HRPP utilizes a checklist to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with Children's Wisconsin's standards. To support compliance, Children's Wisconsin will make every effort to ensure as much consistency as possible across reliance agreements.

Requests for Children's Wisconsin to rely upon an external IRB should be submitted as early as possible in the grant/contract process by submitting a reliance request following the instructions posted on the CW HRPP's web pages.

Children's Wisconsin has signed the SMART IRB joinder agreement, which is the preferred reliance agreement platform. When the organizations participating in the research are signatories to the joinder agreement, IRB reliance may be requested and documented utilizing the SMART IRB online reliance platform. In collaboration with the other participating organizations, Children's Wisconsin will determine on a study-by-study basis whether the SMART IRB SOPs or alternative procedures will be utilized to implement the reliance.

6.1 Children's Wisconsin Serving as Reviewing IRB

Children's Wisconsin does not have an internal IRB and will not serve as the IRB of record for an external organization.

6.2 External IRB Review of Children's Wisconsin Research

All non-exempt human subject research that Children's Wisconsin is engaged in must be reviewed and approved by the designated MCW pediatric IRB or an external IRB that Children's Wisconsin has agreed to rely upon prior to the initiation of the research. See Section 1.8 for information regarding engagement.

In addition to the MCW pediatric IRBs, Children's Wisconsin has standing agreements in place to engage the services of external IRBs for the review of specific categories of research including:

1. NCI's Pediatric CIRB for NCI research involving children
2. NMDP (National Marrow Donor Program)

Research that falls within the above parameters must be registered with Children's Wisconsin prior to submission to the external IRB following the procedures outlined in Section 6.2.2. Post-approval requirements are summarized in Section 6.2.3.

6.2.1 Decision to Rely on an External IRB other than MCW Pediatric IRB (Step 1)

Children's Wisconsin may also choose to enter into an agreement to rely upon other external IRBs, most commonly when required as a condition of a grant or contract. Investigators should submit reliance requests as early in the grant/contract process as possible.

Detailed information about the research must be submitted for Children's Wisconsin HRPP local context review through the electronic submission platform by selecting reliance request in the electronic system and completing all applicable sections.

Children's Wisconsin HRPP evaluates the following factors, and others as appropriate, when considering a request to rely upon an external IRB:

1. The accreditation status of the proposed IRB;
2. The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions);
3. Prior experience with the IRB;
4. The federal IRB registration and organizational FWA, as applicable;
5. The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s));
6. The research activities that will be conducted at or by Children's Wisconsin;
7. The risks and complexities of the proposed research;
8. The proposed reliance terms and procedures including the procedures for collaborative management of matters such as conflicts of interest, noncompliance, unanticipated problems, and federal reports;
9. The plan for review and allowance of the incorporation of site-specific consent language; and

10. The plan for incorporation of other relevant local requirements or context information in the review process.

When reliance on a non-accredited IRB is proposed, the evaluation may also take into consideration one or more of the following based upon the risks of the research, the research activities Children's Wisconsin will be involved in, and Children's Wisconsin's familiarity with the IRB:

1. When the research is minimal risk (or the activities that Children's Wisconsin is involved with are minimal risk), a statement of assurance from the proposed IRB that its review will be consistent with applicable ethical and regulatory standards, and that it will report any regulatory investigations, citations, or actions taken regarding the reviewing IRB, and, when applicable, to the organization's FWA;
2. An attestation about, or summary of, any quality assessment of the reviewing IRB such as evaluation by an external consultant or internal evaluation of compliance using the FDA's self-evaluation checklist or AAHRPP's self-evaluation instrument;
3. The willingness of the external IRB to accommodate requests for relevant minutes and other records of the proposed study and/or to copy Children's Wisconsin's HRPP office on correspondence such as determination letters and notices of suspensions or terminations of IRB approval;
4. The willingness of the external IRB to accommodate a request for someone from the relying organization to serve as a consultant to the IRB or to observe the review of the proposed study; and/or
5. An assessment of the external IRB's policies and procedures.

All determinations and requirements of the external IRBs are equally binding to Children's Wisconsin investigators. Investigators must be familiar with and comply with the external IRB's policies and procedures and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). Children's Wisconsin will support compliance with the terms of reliance agreements by providing investigators with information relevant to their responsibilities, such as a copy or summary of the agreement, an information sheet, or reliance SOPs.

Following evaluation, when the Children's Wisconsin HRPP agrees to rely on an external IRB, written documentation of the decision to rely and that the local materials are cleared for submission to the external IRB is provided in the electronic submission platform (known as 'Step 1 Decision to Rely Letter').

Regardless of which IRB is designated to review a research project, Children's Wisconsin is responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, and oversight by Children's Wisconsin and must adhere to all applicable policies, procedures, and requirements, including those of the Children's Wisconsin HRPP.

6.2.2 Registration of Studies Reviewed by External IRBs (known as 'Step 2' or 'shadow submission') for Local Context Review

Once a decision is made to rely on an external IRB the CW HRPP staff will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed and will determine the need for relaying local context information to the reviewing IRB in accordance with the reliance agreement.

When applicable, and when the external IRB is not responsible for reviews of requests for waivers or alterations of HIPAA authorization (e.g., studies reviewed by the NCI CIRB), the HRPP staff will forward requests for waiver or alteration of HIPAA authorization and any relevant materials to the internal Privacy Board Chair or a designee.

Once approved by the external IRB, investigators must submit a copy of the approval notice for addition of CW and any approved consent document(s) to the HRPP office via the electronic system. If the protocol was modified during the external IRB review process, the approved version of the protocol should be provided as well. Following confirmation of the approval a final letter notifying the PI that the research can begin locally will be sent via the electronic submission system ('Step 2 –"Green Light Letter").

6.2.3 Post-Approval Requirements

While research conducted at Children's Wisconsin is under the purview of an external IRB, Children's Wisconsin HRPP will continue to review study progress, protocol modifications, reportable events, and new information about the project from an institutional and local context perspective.

Investigators approved through external IRB review must still report local unanticipated problems, complaints, and noncompliance (See Sections 17, 18, & 19 of this manual) to the Children's Wisconsin HRPP office via the electronic system in addition to reporting to the external IRB of record in accordance with their submission process and platform. Copies of the report submitted to the external IRB are generally acceptable, but additional information may be requested on an as-needed basis. Investigators must also submit copies of continuing review reports, updated protocols, updated consent forms, study closures, and the corresponding IRB approval or acknowledgment.

NOTE: Children's Wisconsin HRPP office has access to the submission and materials for Continuing Review within the eBridge system. When the MCW Pediatric IRB is the IRB of record for a research project and the CPR, as well as other post approval submissions such as reportable events, are submitted via eBridge, there is no need to submit anything additional for the CW HRPP.

Changes in PI and the addition of other research team members must be submitted to the HRPP office via the electronic system prior to the new PI or research team member assuming any study responsibilities. The HRPP office must verify CITI training, COI review, and any other applicable requirements.

Notices about and reports from external monitors, auditors, or inspectors must be provided to the HRPP office as described in Section 2.1 of this manual.

Any of the following issues must be reported immediately (ASAP once aware) to the Children's Wisconsin HRPP office by phone or email:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after the FDA has the opportunity to review any responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;
- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding Children's Wisconsin's HRPP.

Investigators are reminded that other Children's Wisconsin reporting requirements, such as to Compliance, Privacy, and Risk Management, remain applicable in addition to HRPP reporting requirements.

6.3 Single IRB (sIRB) Mandate for Multi-Site or Cooperative Research

Non-exempt, federally funded multi-site or cooperative research requires review by a Single IRB (sIRB) as described below.

NIH considers research to be **multi-site** when the same protocol is conducted at more than one location.

As per the revised Common Rule, research is **cooperative** when a single project involves more than one institution.

NIH Single sIRB Requirement

In June 2016, the National Institutes of Health (NIH) released a final policy requiring domestic awardees and domestic sites of NIH-funded multi-site research to use a single IRB (sIRB) for review of non-exempt human subject research unless an exception is granted. This policy is intended to streamline the IRB review process and reduce inefficiencies and redundancies while maintaining and enhancing subject protections. The NIH policy does not apply to career development, research training, or fellowship awards,) nor does it apply to research sites outside of the US. However, sIRB may still be required for domestic sites under the Cooperative Research provisions of the revised Common Rule (see below).

Exceptions to the NIH policy are rare. Information regarding exception requests is available on NIH's Single IRB website.

Common Rule sIRB Requirement

The January 21, 2020 Common Rule Cooperative Research regulation requires single IRB review for domestic sites engaged in cooperative, non-exempt human subjects research that involves

multiple institutions and is sponsored by signatories of the revised Common Rule. All sites in the US that are engaged in a federally funded cooperative research project subject to the revised Common Rule must rely upon approval by a sIRB for that portion of the research that is conducted in the US.

Exceptions to the Common Rule Cooperative Research provision include:

- Participating sites located outside of the United States.
- Research that requires individual IRB review by law (e.g., American Indian or Alaskan Native tribal law).
- Research for which a federal agency determines and documents that the sIRB model is not appropriate. Information regarding federal agency exception requests for HHS-supported research is available on OHRP's Single IRB Exception Determinations website.
- Research funded by the Department of Justice since DOJ/NIJ/OJP is not currently a signatory of the revised Common Rule.

sIRB is Not Required for Exempt Research

Common Rule and NIH requirements for single IRB review **do not** apply to exempt research, including exempt research for which limited IRB review takes place. When an organization opts to rely upon another IRB for the review of exempt research with limited IRB review, the agreement to do so must be documented as described in 6.3.2.

6.3.1 Selection and Designation of a sIRB

Children's Wisconsin's investigators must plan in advance for sIRB review when developing applications for non-exempt federally-funded multi-site or cooperative research.

For NIH multi-site research, investigators may request direct cost funding to cover additional costs related to the requirements of the NIH policy. Other Federal funding agencies may not allow these fees as a direct cost.

The NIH requires that the name of the sIRB is provided at Just-in-Time (JIT) or, for delayed-onset research when a sIRB has not yet been identified, the sIRB name must be provided to the funding Institute/Center prior to initiating the non-exempt multi-site research.

A formal single IRB plan may not be required for proposals to other Federal funding agencies. Investigators are encouraged to consult with their program officer regarding what information about single IRB review should be included in their non-NIH application. The lead institution may propose a sIRB, but the Federal department or agency supporting the research is ultimately responsible for naming the sIRB.

In all circumstances, the named IRB must have agreed to take on this responsibility in advance.

Requests for Children's Wisconsin to rely upon an external IRB as the sIRB should be submitted as early in the process as possible as described in Section 6.2.1.

6.3.2 Reliance Agreements for sIRB Studies

A Reliance Agreement (or "Authorization Agreement") between the sIRB and the participating sites is required. The Reliance Agreement documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.

Reliance Agreements should describe the responsibilities of all parties and how communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval. When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing), the agreement or written procedures should indicate who is responsible for meeting the certification requirements.

The institution that is awarded the funding for the research is responsible for maintaining all agreements and for ensuring that adequate and appropriate communication channels between the sIRB and participating sites are in place. Participating sites are responsible for maintaining copies of the site agreement in accordance with the terms of their FWA.

6.4 Responsibilities

The sIRB will be responsible for compliance with the regulatory requirements for IRBs specified in the federal regulations (i.e., 45 CFR 46 and other applicable regulations) and for any other responsibilities outlined in the reliance agreement and/or procedures. Participating sites (Relying institutions) are responsible for providing relevant local context information to the sIRB, ensuring that the research is conducted in accordance with applicable regulations and the determinations and requirements of the sIRB, and for other responsibilities, as outlined in the reliance agreement and/or procedures.

When an external IRB serves as the sIRB for a study Children's Wisconsin is engaged in, investigators must register the study with Children's Wisconsin prior to submission to the external IRB following the procedures outlined in Section 2.1. Post-approval requirements are summarized in Section 2.2.

Research reviewed by external IRBs remains subject to review, approval, and oversight by Children's Wisconsin and must adhere to all applicable policies, procedures, and requirements, including those of the Children's Wisconsin HRPP.

7 Research Previously Approved by Another IRB – Not Applicable

Not applicable at the current time because Children's Wisconsin IRB is not reviewing new studies effective July 1, 2022.

8 HRPP Emergency Preparedness, Continuity and Recovery (Domain I)

In the event of an emergency or disaster (e.g., public health or weather-related), the procedures in these SOPs may be modified as appropriate for the situation. Such modifications

may include alternative meeting procedures, alternative procedures for the submission and review of modifications, alternative procedures for prompt reporting, and any other changes necessary to ensure appropriate ongoing oversight and conduct of research. Because procedural modifications may vary based on the nature of the event, these cannot be anticipated and described in these SOPs. Instead, such procedural modifications will be recorded in an addendum to the SOPs, note-to-file, or other appropriate means of documentation and communicated to the research community. This documentation will be maintained in accordance with applicable record retention requirements.

9 Institutional Review Board (AAHRPP Domain II)

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

10 IRB Actions, Failure to Respond, Appeals (AAHRPP Domain II)

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

11 IRB Review Process (AAHRPP Domain II)

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

12 Suspensions, Terminations, and Investigator Holds (AAHRPP Domains I and II)

The Children's Wisconsin HRPP has granted the IRBs of record serving for Children's Wisconsin authority to suspended or terminate IRB approval if research is not being conducted in accordance with the IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. The IRB's authority to suspend or terminate research applies to all research subject to IRB approval, including research for which continuing review is no longer required.

The Institutional Official (see section 1.11.1) has the authority to suspend or terminate the organization's approval for research. Such actions will be promptly reported to the IRB of record so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight.

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

13 IRB Documentation and Records (AAHRPP Domain II)

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

14 Obtaining Informed Consent from Research Subjects (AAHRPP Domain II)

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the federal regulations and Children's Wisconsin HRPP. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR unless the requirement has been waived by the IRB of record. When informed consent is required, it must be sought prospectively, and properly documented. Except as provided in Sections 14.8, 14.9, and 14.10 of these procedures, informed consent must be documented using a written consent form approved by the IRB.

The Children's Wisconsin HRPP and the IRB of record will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants. The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. The informed consent process is the critical communication link between the prospective human subject and an investigator, beginning with the initial approach and continuing through the completion of the research study (the recruitment plan must be described and approved by the IRB of record.) The process of obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB. See Section 14.8 for an exclusion for certain screening and recruitment activities.

If someone other than the principal investigator obtains consent, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. Consent delegates must be knowledgeable about the research to be conducted and the consent process and must have the expertise to be able to answer questions about the study including those regarding risks, procedures, and alternatives. The IRB of record application solicits information regarding who will obtain consent; and proposed changes to the personnel authorized to obtain consent must be submitted to the IRB of record for approval. CW HRPP will also review and approve personnel during local context review.

Sample or draft consent documents may be developed by a sponsor or network. However, the CW HRPP and the IRB of record is the final authority on the content of the consent documents that are presented to prospective subjects.

The following procedures describe the requirements for obtaining consent from subjects in research conducted under the auspices of Children's Wisconsin.

14.1 General Requirements

Except as provided elsewhere in these Standard Operating Procedures:

For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

For research subject to the revised Common Rule (2018 requirements):

1. Before involving a human subject in research, an investigator shall obtain the legally effective informed consent of the subject or the subject's LAR
2. An investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence
3. The information that is given to the subject or the LAR shall be in language understandable to the subject or the LAR
4. The prospective subject or the LAR must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information
5. Except for broad consent (See Section 14.13):
    a. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension
    b. Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate

6. No informed consent may include any exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

These informed consent requirements are not intended to preempt any applicable federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that have additional requirements for informed consent to be legally effective.

14.2 Additional Requirements

Informed consent must be obtained under the following circumstances:

1. Informed consent may only be obtained from subjects who have the legal and mental capacity to give consent. For subjects without that capacity, permission must be obtained from a legal guardian with appropriate authority to make decisions regarding the activities called for in the research or a legally authorized representative (LAR);
2. The informed consent information must be presented in language that is understandable to the subject (or LAR/guardian). To the extent possible, the language should be understandable by a person who is educated to 6th grade level and layman's terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population;
3. For subjects with Limited English Proficiency (LEP), informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the Children's Wisconsin HRPP requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent, and, in most circumstances, that consent materials are translated. For more information about enrollment of subjects with LEP, please see the guidance *Consent of Subjects with Limited English Proficiency*.
4. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

14.3 Legally Authorized Representative (LAR)

This section applies to adults who are not capable of providing informed consent and a legally authorized representative will be used to provide consent on behalf of the subject.

A Legally Authorized Representative (LAR) is defined by 45 CFR 46.102(c) and 21 CFR 50.3 as *"an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research."* If there is no applicable law addressing this issue, LAR means an individual recognized by institutional policy as acceptable for providing consent in the non-research context on behalf of

the prospective subject to the subject's participation in the procedure(s) involved in the research.

Who may serve as LAR is determined by state law. Wisconsin law (Wis. Stat. 54.25.d.2) generally permits the LAR to do the following (however, a court granting guardianship may limit these powers):

Unless it can be shown by clear and convincing evidence that the ward would never have consented to research participation, the power to authorize the ward's participation in an accredited or certified research project if the research might help the ward; or if the research might not help the ward but might help others, and the research involves no more than minimal risk of harm to the ward. The power to authorize the ward's participation in research that might not help the ward but might help others even if the research involves greater than minimal risk of harm to the ward if the guardian can establish by clear and convincing evidence that the ward would have elected to participate in such research; and the proposed research was reviewed and approved by the research and human rights committee of the institution conducting the research. The committee shall have determined that the research complies with the principles of the statement on the use of human subjects for research adopted by the American Association on Mental Deficiency, and with the federal regulations for research involving human subjects for federally supported projects.

Due to the variable nature of guardianship rights, CW legal and the CW HRPP should be consulted on a case by case basis.

Wisconsin law does not specifically address informed consent by LARs of incapacitated persons for participation in clinical research. Thus, the applicable guidelines for determining the most appropriate LAR for research are based upon the guidelines that apply in the clinical setting.

For legally incompetent adults who are unable to make medical decisions, a legal representative (court appointed guardian) or durable power of attorney for health care must provide informed consent for non-emergent medical treatment. The legal guardian must be authorized by the court to make decisions regarding the types of activities, procedures, or treatments called for in the research to serve as LAR. Substitute decision-makers, as defined in Children's Wisconsin's clinical informed consent policy (*CHHS Policy - Consent for Treatment)* may serve as LAR for research involving clinical procedures or treatments when a court appointed guardian or durable power of attorney for health care are not in place.

LARs should be well informed regarding their roles and responsibilities when asked to provide surrogate consent. In addition to the consent information, LARs should be informed that their obligation is to try to determine what the potential subject would do if able to provide consent, or if the potential subject's wishes cannot be determined, what they think is in the person's best interest.

Investigators must describe the intended use of LARs in their submission to the IRB. The IRB of record determines whether the use of LARs is appropriate for a given research study.

Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in Section 15.7.

14.4 Basic Elements of Informed Consent

Note: This section does not apply for broad consent obtained as described in Section 14.13.

To be valid, the consent process must provide the following basic elements of information to potential subjects:

1. A statement that the **study involves research**, an explanation of the **purposes** of the research and the **expected duration** of the subject's participation, a description of the **procedures** to be followed, and identification of any **procedures which are experimental**;
2. A description of any reasonably foreseeable **risks or discomforts** to the subject;
3. A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which **confidentiality** of records identifying the subject will be maintained;
6. **For research involving more than minimal risk**, an explanation as to whether any compensation **and** an explanation as to whether any medical treatments are available if injury occurs **and**, if so, what they consist of, or where further information may be obtained;
7. An **explanation of whom to contact** for answers to pertinent questions about the research **and** research subjects' rights, **and** whom to contact in the event of a research-related injury to the subject;
8. Contact information for the research team for questions, concerns, or complaints.
9. Contact information for someone independent of the research team for problems, concerns, questions, or input.
10. A statement that participation is **voluntary**, refusal to participate will involve **no penalty or loss of benefits** to which the subject is otherwise entitled, and the subject **may discontinue participation** at any time without penalty or loss of benefits to which the subject is otherwise entitled;
11. **For research subject to the revised Common Rule (2018 requirements):** One of the following statements about any research that involves the **collection of identifiable private information or identifiable biospecimens**:
    a. A statement that **identifiers might be removed** from the identifiable private information or identifiable biospecimens **and that**, after such removal, the information or biospecimens **could be used** for future research studies or distributed to another investigator for future research studies **without**

additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, **will not be used or distributed** for future research studies.

12. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
13. For applicable **FDA-regulated clinical trials,** the following statement must be included verbatim:

    "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

14.5 Additional elements of informed consent to be applied, as appropriate:

Note: This section does not apply for broad consent obtained as described in Section 14.13.

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. When applicable, the amount and schedule of all payments;
5. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
6. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
7. The approximate number of subjects involved in the study;
8. **For research subject to the revised Common Rule (2018 requirements):**
    a. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;
    b. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;

c. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

14.6 Children's Wisconsin Requirements

14.6.1 Local Language

In addition to the federal regulatory elements of consent described above, Children's Wisconsin has defined specific additional information that must be included in consent documents when applicable to the research (e.g., 1099 language). This language is included in the MCW consent templates, the boilerplate language approved by various cooperative groups, and consent template module to be inserted in the sample consent when working with another IRB of record. Children's Wisconsin HRPP reviews template language change requests and has the authority to require changes to the approved consent document.

14.6.2 Acceptable Alternative Method to Obtain Consent: Remote Process and Documentation

In situations where there cannot be face-to-face interaction with subjects, CW HRPP allows for the consent process to be conducted remotely. Informed consent must include a discussion of required elements as detailed above, and in most cases, is not valid consent until the subject has signed and dated the consent.

If researchers would like to request approval of a remote process for obtaining assent/consent/parental permission, the following should be kept in mind:

a. Acceptable means of transmitting documents include sending by encrypted email, faxing consent documents to and from, or using traditional services such as USPS mail/priority mail, FedEx, UPS, and courier. Note: Non-encrypted email and text messaging are not acceptable methods of transmitting study consent forms.
b. There must still be a verbal consent discussion with the potential subject/family with the opportunity for them to ask questions, and for the research team to assess their understanding. This can be done via phone or other "real time" HIPAA-compliant communication platform (such as Zoom).
c. The potential subject/family must have a copy of the consent documents in hand for reference during the discussion.
d. Unless the IRB has waived documentation (the signature), all signed documents must be received by the researcher prior to initiating any study-related procedures.
e. The provider who conducted the consent discussion should sign and date the documents recording the date received.
f. Consent discussion should be documented in the subject's medical or research record on the date it occurred.

14.7 Subject Withdrawal or Termination

A subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research plans and consent documents.

When seeking informed consent from subjects, the following information regarding data retention and use must be included:

1. **For FDA-regulated clinical trials:** When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. This should be disclosed in the consent; or
2. **For research not subject to FDA regulations:** The investigator should inform subjects whether the investigator or study sponsor intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject's request that the investigator or study sponsor will destroy the subject's data or that the investigator or study sponsor will exclude the subject's data from any analysis.

When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject wishes to participate in continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review.

If a subject withdraws from the interventional portion of the study but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

14.8 Documentation of Informed Consent

Except as provided in Sections 14.10, 14.11 and 14.12 of this manual, informed consent must be documented by the use of a written consent form approved by the IRB of record.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed (including in an digital format) and dated by the subject or the subject's LAR at the time of consent; A dynamic signature (a handwritten but digitally captured signature made on a touch device such as a tablet or smartphone) is acceptable. Requests for other types of electronic signatures will be assessed on a case-by-case basis. Children's Wisconsin continues to evaluate what types of electronic signatures are acceptable.
2. For research conducted in accordance with ICH-GCP E6 or in facilities subject to Joint Commission requirements, the name of the person who obtained consent and the date they did so is documented on the written consent form;
3. A written copy of the consent form must be given to the person signing the form. The investigator should retain the signed original in the research records. When appropriate, a copy of the consent form is uploaded into the electronic health record;

The consent form may be either of the following:

1. **For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:** A written consent document that embodies the basic and required additional elements of informed consent. The consent form may be read to the subject or the subject's LAR, but the subject or LAR must be given adequate opportunity to read it before it is signed;

   For research subject to the revised Common Rule (2018 requirements): A written consent document that embodies the basic and required additional elements of informed consent. The investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's LAR;

   or

2. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR (**For research subject to the revised Common Rule:** and that the key information required by Section 14.1 #5.a was presented first to the subject, before other information, if any, was provided). When this method is used:
   a. The oral presentation and the short form written document should be in a language understandable to the subject; and
   b. There must be a witness to the oral presentation; and
   c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
   d. The short form document is signed by the subject;
   e. The witness must sign both the short form and a copy of the summary; and
   f. The person actually obtaining consent must sign a copy of the summary; and

g. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.

Per FDA's Final Guidance on Informed Consent, it is recognized that investigators on occasion face circumstances where: (1) a prospective subject who does not understand English is eligible for an IRB-approved research protocol; and (2) the investigator has an IRB-approved English language long form but does not have an appropriate IRB-approved written translation of the long form or written summary for the study. This may occur because neither the investigator nor the IRB reasonably expected enrollment of a subject for whom a translation would be needed.

For some research, the timeframe for subject enrollment may provide sufficient time for the preparation of an appropriately translated long form or an appropriately translated written summary to be used with a short form. When translation or interpretation is needed for written and oral information that is to be presented to subjects, FDA recommends and the CW HRPP expects that the IRB review, and if appropriate, approve reasonable procedures for ensuring that the translations will be prepared by a qualified individual or entity, and that interpretation assistance is available.

When the short form procedure is used with subjects who do not speak or read English, or have Limited English Proficiency (LEP), (i) the oral presentation and the short form written document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject. When the person obtaining consent is assisted by an interpreter, the interpreter may serve as the witness.

The witness must be present physically or by some other means, for example, by phone or video conference, during the oral presentation, not just the signing of the consent form (21 CFR 50.27(b)(2)). The purpose of the witness is generally to attest to the voluntariness of the subject's consent and the adequacy of the consent process by ensuring that the information was accurately conveyed and that the subject's questions were answered

The IRB of record must receive all foreign language versions of the short form document as a condition of approval. The investigator must obtain a translated copy of the IRB-approved English version of the long form that served as the written summary, which should be done promptly. The investigator promptly (within 30 days) submits it to the IRB for review and approval. Once the translated long form/written summary is approved by the IRB, the investigator must provide it to the subject or LAR and should do so as soon as possible. FDA considers this step essential to the requirement that informed consent be documented by the use of a written consent document and that the subject be provided a copy (21 CFR 50.27). Many of the clinical investigations regulated by FDA involve ongoing interventions and may involve long-term follow-up. For this reason, translation of the long form is critically important as a means of providing subjects or their LAR an ongoing source of information understandable to them.

Expedited review of these versions is acceptable if the protocol/research plan, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

For more information about enrollment of subjects with limited English proficiency, please see CW HRPP webpage Consent/Parental Permission/Assent of Subjects with Limited English Proficiency and Guidance – Consent of Subjects with Limited English Proficiency.

Special Consent Circumstances

Federal regulations and guidance recognize the need for flexibility in the consent process and documentation of consent, particularly to support equitable selection of subjects and access to research that may offer benefit. The following content is intended to help investigators navigate certain circumstances that may impact how consent is obtained and documented but is not exhaustive. Investigators are encouraged to contact the HRPP office with any questions they have about obtaining and documenting consent.

14.8.1 Electronic Informed Consent (eIC)

The ethical obligation to obtain informed consent for participation in research is fundamental; however, U.S. regulations do not specify a particular method for the informed consent process. Recognizing the increased interest in using electronic informed consent (eIC) to replace or supplement the traditional paper-based process, OHRP and FDA issued joint guidance on the topic in 2016. Per the guidance, eIC refers to *"the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent."* Investigators planning to use eIC should review the guidance in advance to ensure that the eIC process and platform meet OHRP and FDA (as applicable) expectations.

Investigators proposing to use eIC should submit copies of all forms and informational materials (e.g., video content, hyperlinked webpages) that the potential subject will review during the eIC process. If the eIC includes questions or other methods to gauge subject comprehension, these should also be provided. Investigators are responsible for periodically reviewing any links to materials to ensure that the content remains available and is unchanged. Any changes to the eIC or any of the supplemental information must be submitted to the IRB for review and approval.

Whether the eIC process takes place in person or remotely, the responsibility for obtaining informed consent remains with the investigator and any appropriately delegated study team members. When the eIC process takes place remotely and is not witnessed by the investigator or study team members, the eIC generally should include a method to ensure that the person electronically signing the eIC is the subject or their LAR, when applicable. Exceptions to this general rule may be acceptable in certain circumstances (e.g., minimal risk research).

As with any other form of consent, the eIC process must allow for sufficient time for the potential subject to consider whether to participate and must include a mechanism for

potential subjects to ask questions and have them answered. A copy of the eIC must be provided to participants, including copies of any supplemental materials. The copy provided to participants may be hardcopy or electronic.

Electronic signatures must be compliant with applicable legal requirements, including those of the jurisdiction where the research is to be conducted, and the FDA's requirements, when applicable.

14.8.2 Enrollment of persons with Limited English Proficiency

1. **Expected enrollment**: In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document and other subject materials, as applicable. Generally, translated consent forms should not be prepared until the final approved version of the English-language version is available. To ensure that translated documents are accurate, the HRPP requires a certified translation, and the IRB may additionally require an independent back-translation, or to have a review of the translated documents by an IRB member or other person who is fluent in the language.

2. **Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English unexpectedly presents for possible enrollment, an IRB-approved translated version of the written consent document may not be available for use. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed or legally effective.

   If an investigator decides to enroll a subject into a study for which there is not an extant IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a "short form" written consent in as described in this manual.

   Note: For studies that are not FDA regulated CW HRPP allows the use of the "short form" process for one subject without the need to follow up with a full translation of the English consent document serving as the summary to be provided to the subject. However, any additional enrollments on the same study of subjects with limited English proficiency of the same language for which the short form was used previously, will require an IRB approved translation of the full consent, as it is no longer unexpected.

3. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject's language, an interpreter will be necessary to facilitate the consent discussion. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or

short form and the IRB-approved consent script (typically the English-language version of the consent document), well before (24 to 48 hours if possible) the consent discussion with the subject. If the interpreter also serves as the witness, s/he may sign the translated consent, or short form consent document and script, as the witness and should note “Interpreter” under the signature line. The person obtaining consent must document that the “short form” process was used in the subject's research record, including the name of the interpreter.

14.8.3 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) has the ability to understand the concepts of the study and evaluate the risks and benefits of being in the study when it is explained orally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 14.8.

For greater than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audiotape approved by the IRB may also be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide oral consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and that the subject gave oral consent or made their mark. The consent process will also be documented in the subject’s research record. Signed copies of the consent form are given to the subject.

14.8.4 Physically Challenged Subjects

A person who is physically challenged (e.g., physically unable to talk or write) can enroll in research if competent and able to indicate voluntary consent to participate. Whenever possible, the subjects should sign the consent form or make their mark by initialing or making an X. As with oral consent, a witness to the consent process is recommended and the circumstances and consent process should be carefully documented in the research records.

14.9 Waiver or Alteration of Informed Consent

General Waiver or Alteration:

For research subject to the pre-2018 Common Rule, or FDA or DOJ regulations:

An IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research or clinical investigation involves no more than minimal risk to the subjects;

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research or clinical investigation could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Note: Prior to January 22, 2024, waivers or alterations for certain FDA-regulated research may have been granted by an IRB in accordance with these criteria based on the July 25, 2017 FDA guidance" IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects" (82 FR 34535)

For research subject to the revised Common Rule (2018 requirements) and/or FDA 50.22 (effective January 22, 2024):

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied**. For research subject to the revised common Rule (2018) requirements:** An IRB **may not** waive or alter broad consent (See Section 14.11), nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent in accordance with Section 14.11 and refused.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration"), provided that the IRB finds and documents that the below criteria are satisfied. **For research subject to the revised common Rule (2018) requirements:** An IRB **may not** omit or alter any of the general requirements for informed consent (See Section 14.1).

1. The research or clinical investigation involves no more than minimal risk to the subjects;
2. The research or clinical investigation could not practicably be carried out without requested waiver or alteration;
3. If the research or clinical investigation involves using identifiable private information or identifiable biospecimens, the research or clinical investigation could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, the subjects or LARs will be provided with additional pertinent information after participation.

Public Benefit or Service Programs Waiver or Alterations

For research subject to the pre-2018 Common Rule or DOJ regulations:

(Note: this option is <u>not</u> available to research subject to FDA regulations)

In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs; and,
2. The research could not practicably be carried out without the waiver or alteration.

For research subject to the revised Common Rule (2018 requirements):

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent (See Section 14.11), nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent in accordance with Section 14.11 and refused.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration") (See Sections 14.4 and 14.5), provided that the IRB finds and documents that the below criteria are satisfied. An IRB **may not** omit or alter any of the general requirements for informed consent (See Section 14.1).

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.

14.9.1 Screening, recruiting, or determining eligibility

For additional information please see the CW HRPP Guidance entitled *Recruitment for Human Subject Research.*

For research subject to the revised Common Rule: An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

1. The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
2. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

*(**Note:** The provisions described in this section do not apply to research subject to the **pre-2018 Common Rule or to DOJ-regulated research**. These provisions do not appear in FDA regulations, however, the FDA does not consider records review or oral communication with potential subjects prior to obtaining consent to be part of a clinical investigation; therefore waivers are not required. See FDA Draft Guidance for more information.)*

14.10 Waiver of Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds **any** of the following:

1. The only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm from a breach of confidentiality (e.g., domestic violence research where the primary risk is discovery by the abuser). Each subject (or LAR) will be asked whether they want documentation linking them with the research, and their wishes must govern.

   This option **does not** apply to FDA-regulated research.

OR

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-investigators (e.g., marketing surveys, telemarketing).

   This option **does** apply to FDA-regulated research (most commonly in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in a clinical trial).

OR

3. If the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

   This option **does not** apply to research subject to the **pre-2018 Common Rule or to FDA or DOJ** regulations.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an appropriate consent process.

In cases in which the documentation requirement is waived, the IRB requires the investigator to provide in the application materials a written summary of the information to be communicated to the subject, and the IRB will consider whether to require the investigator to provide subjects with a written statement regarding the research.

14.11 Waiver of Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergencies where the requirement to obtain prospective informed consent has been waived by the IRB is covered by 21 CFR 50.24 for FDA-regulated research and by the waiver articulated by DHHS at 61 FR 51531-33 for research that is not FDA-regulated.

The FDA exception from informed consent requirements for emergency research under FDA regulations permits planned research in an emergency setting when human subjects who are in need of emergency medical intervention cannot provide legally effective informed consent themselves, and there is generally insufficient time and opportunity to locate and obtain consent from their legally authorized representatives (LARs).

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under 45 CFR 46.101(i) with provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 14.10.2.1 and 14.10.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

14.11.1 Definitions

Planned Emergency Research. It is research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, it is generally not possible to obtain legally effective informed consent.

Family Member. For this section, a legally competent adult with one of the following relationships to the subject: spouse; parent; child (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

14.11.2 Procedures

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

The IRB of record may approve the planned emergency research without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions have been met:

1. The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
2. Obtaining informed consent is not feasible because:
    a. The subjects will not be able to give their informed consent as a result of their medical condition;
    b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
    c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
    a. Subjects are facing a life-threatening situation that necessitates intervention;
    b. Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
    c. Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. The research could not practicably be carried out without the waiver.
5. The proposed research plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB of record at the time of continuing review.
6. The IRB of record has reviewed and approved informed consent procedures and an informed consent document consistent with Sections 46.116 and 46.117 of 45 CFR 46

and Sections 50.20, 50.25 and 50.27 of 21 CFR 50. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research consistent with paragraph 7.e. of this section.

7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
    a. Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the research will be conducted and from which the subjects will be drawn;
    b. Public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;
    c. Public disclosure of sufficient information following completion of the research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
    d. Establishment of an independent data monitoring committee to exercise oversight of the research; and
    e. If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, the IRB of record is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

14.11.2.1 FDA-regulated Planned Emergency Research

A licensed physician who is a member of or consultant to the IRB of record and who is not otherwise participating in the clinical investigation must concur that the conditions described in this section are satisfied.

Studies involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies that such studies may include subjects who are unable to consent. The submission of those studies in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for such investigations may not be submitted as amendments under 312.30 or 812.35.

If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

The IRB determinations and documentation required in this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b).

14.11.2.2 Documentation and Reporting of Planned Emergency Research Not Subject to FDA Regulations

The IRB of record responsible for the review, approval, and continuing review of the research must approve both the research and a waiver of informed consent and have (i) found and documented that the research **is not** subject to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented **and** reported to the OHRP that the conditions required in this section have been met relative to the research.

14.12 Elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens

RESERVED – at this time, Children's Wisconsin does not allow broad consent for secondary research.

14.13 Posting of Clinical Trial Consent Forms

For research subject to the revised Common Rule (2018 requirements):

For each clinical trial conducted or supported by a Federal department or agency, one IRB approved informed consent form used to enroll subjects **must be posted by the awardee or**

the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g., confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

At this time, two publicly available federal websites that will satisfy the consent form posting requirement have been identified: ClinicalTrials.gov and a docket folder on Regulations.gov (Docket ID: HHS-OPHS-2018-0021). Additional federal websites that would satisfy the revised Common Rule's clinical trial consent form posting requirement might be identified in the future.

See MCW Clinical Trials Office for instructions to post the informed consent form.

15 Vulnerable Subjects in Research (Domain II)

When participants in research conducted under the auspices of Children's Wisconsin are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of subjects are met and that appropriate additional protections for vulnerable subjects are in place.

15.1 Definitions

Children. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.402(a)].

According to Wisconsin State Law, minors are persons under the age of eighteen. The general rule is that a person may sign legally-binding agreements and consent for his or her own medical care at the age of eighteen. Therefore, CW defines children as persons who are under eighteen years of age. Wisconsin considers any minor that is married, has joined the armed forces as emancipated. A Wisconsin court may also emancipate a minor is special circumstances. Any emancipated minor may direct their own care as if they were adults. Wisconsin law also permits minors to seek and receive care in certain circumstances without parental consent. None of these circumstances are research in and of itself, however, some of the procedures involved in research may consist of these circumstances. Children's Wisconsin Legal counsel and the CW HRPP should be consulted for a case by case determination

NOTE: For research conducted in jurisdictions other than Wisconsin the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel will

be consulted with regard to the laws in other jurisdictions or such "local context" information will be sought through other mean (e.g., according to the terms of a reliance agreement).

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care [45 CFR 46.402(e)].

In Wisconsin a "Guardian" of a child means a court-appointed person with the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his or her general welfare (Wis. Stat. 54.25).

NOTE: For research conducted in jurisdictions other than Wisconsin the research must comply with the laws regarding guardianship in all relevant jurisdictions. Legal counsel will be consulted with regard to the laws in other jurisdictions or such "local context" information will be sought through other means (e.g., according to the terms of a reliance agreement).

Fetus. A fetus means the product of conception from implantation until delivery [45 CFR 46.202(c)].

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord [45 CFR 46.202(a)].

Delivery. Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means [45 CFR 46.202(b)].

Neonate. A neonate is a newborn [45 CFR 46.202(d)].

Viable. As it pertains to the neonate, viable means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration [45 CFR 46.202(h)]. If a neonate is viable, then, for the purposes of participation in research, the neonate is considered a child and the rules regarding participation of children in research apply.

Nonviable neonate. A nonviable neonate means a neonate after delivery that, although living, is not viable [45 CFR 46.202(e)].

Pregnancy. Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery [45 CFR 46.202(f)].

Prisoner. Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing [45 CFR 303(c)].

15.2 Involvement of Vulnerable Populations in Research

When the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about and experienced in working with these participants. When the IRB does not have the relevant expertise among its membership, expertise may be sought through the use of consultants.

45 CFR 46 has additional subparts designed to provide extra protections for certain defined vulnerable populations which also have additional requirements for IRBs.

Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D - Additional Protections for Children Involved as Subjects in Research

Non-exempt DHHS-conducted or supported research that involves any of these populations must comply with the requirements of the relevant subparts. Research regulated by the FDA includes equivalent protections and obligations when research involves children (Subpart D). Research conducted, supported, or otherwise regulated by other federal departments or agencies may or may not be covered by the subparts. See the Special Topics section of this manual for additional information on department or agency requirements.

In its FWA, Children's Wisconsin limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.

Note: MCW HRPP applies flexibility to some non-funded activities; however Children's Wisconsin does not extend that flexibility to all Children's Wisconsin research. Any flexibility for Children's Wisconsin research will be described in this SOP manual. Sections that define flexibility are noted with the following: ****FLX**

15.3 Procedures

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

15.4 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the Children's Wisconsin IRB of record. DHHS-specific requirements are noted in the appropriate sections.

If a woman becomes pregnant while participating in a study that has not been approved for inclusion of pregnant women, the IRB must be notified immediately so that the IRB can determine whether the subject may continue in the research, whether additional safeguards are needed, and to make the determinations required by the regulations and these policies.

15.4.1 Research Involving Pregnant Women or Fetuses

15.4.1.1 Research Not Conducted or Supported by DHHS

For research not conducted or supported by DHHS, where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required by policy and there are no restrictions on the involvement of pregnant women in research. However, the IRB of record may determine that additional safeguards or restrictions are warranted for a specific study. ****FLX**

Pregnant women or fetuses may be involved in research not funded by DHHS **involving more than minimal risk** to pregnant women and/or fetuses if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; ****FLX**
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the consent of the pregnant woman is obtained in accordance with the provisions for informed consent;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 15.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB of record; ****FLX**
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research if their involvement in the determination of viability for an individual fetus cannot be avoided. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in

the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB of record and HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days. **FLX

15.4.1.2 Research Conducted or Supported by DHHS

For DHHS-conducted or supported research, 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 15.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 15.6.2;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

15.4.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

15.4.2.1 Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research **involving more than minimal risk** if all of the conditions listed below are met. The IRB will determine on a case-by-case basis whether safeguards or restrictions should be required for minimal risk research.

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to involving the subject(s) in the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB and HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days. ****FLX**
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

The IRB of record determines that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

2. The purpose of the research is the development of important knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; **FLX and
3. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important knowledge that cannot be obtained by other means; **FLX and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a LAR of either or both of the parents of a nonviable neonate will not suffice.

15.4.2.2 Research Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research conducted or supported by DHHS if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
2. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether a neonate is viable, a neonate may not be involved in research unless the following additional conditions have been met:

1. The IRB determines that:
    a. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
    b. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR need not be obtained if the pregnancy resulted from rape or incest.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research unless all of the following additional conditions are met:

1. Vital functions of the neonate will not be artificially maintained;
2. The research will not terminate the heartbeat or respiration of the neonate;
3. There will be no added risk to the neonate resulting from the research;
4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
5. The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions of permission and assent, except that the waiver and alteration of the provisions of permission and assent do not apply.

However, if either parent is unable to consent because of unavailability or incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a LAR of either or both of the parents of a nonviable neonate will not suffice.

15.4.3 Viable Neonates

A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements for research involving children (i.e., a viable neonate is a child for purposes of applying federal research regulations and Children's Wisconsin policies).

15.4.4 Research Involving, After Delivery, the Placenta, the Dead Fetus or Fetal Material

Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, must be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

If information associated with material described above in this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent sections of these policies and procedures are applicable.

15.4.5 Research Not Otherwise Approvable

15.4.5.1 Research Not Conducted or Supported by DHHS

If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the provisions described previously in this section, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). ****FLX** Based on the recommendation of the panel, the IRB may approve the research based on either:

1. That the research in fact satisfies the conditions detailed above, as applicable; or
2. The following:
    a. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
    b. The research will be conducted in accord with sound ethical principles; ****FLX** and
    c. Informed consent will be obtained in accord with the requirements for informed consent described in this manual.

15.4.5.2 Research Conducted or Supported by DHHS

DHHS-conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. If the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and the research is not approvable under the above provisions, then the research will be sent to OHRP for DHHS review.

15.5 Research Involving Prisoners

15.5.1 Applicability

For research not conducted or supported by DHHS, where the risk to prisoners is no more than minimal (as defined in Section 15.5.2), no additional safeguards are required under these policies and procedures. However, the IRB of record may determine that additional safeguards or restrictions are warranted for a specific study. ****FLX**

For research involving more than minimal risk, and for research conducted or supported by DHHS (unless the research is subject to the revised Common Rule, qualifies for exemption, and only incidentally includes prisoners (See Section 5)), the requirements outlined in this section apply.

As applicable, investigators must obtain permission from and abide by the requirements of correctional authorities and federal, state, or local law. **CW legal and the CW HRPP office should be consulted prior to submitting any research involving prisoners**.

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record for details.

15.5.2 Incarceration of Enrolled Subjects

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to these procedures, the investigator must promptly notify the IRB of record and CW HRPP as an Unanticipated Problem. Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record for details.

15.5.3 Certification to DHHS

Under 45 CFR 46.305(c), institutions engaged in research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB of record has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research. Certification is not required for exempt research that only incidentally includes prisoners (see Section 5).

When Children's Wisconsin is responsible for submitting certification to OHRP, the CW HRPP and IRB of record will do so using the web-based certification form available on OHRP's website. The certification form must be accompanied by the "research proposal" which OHRP defines as including:

- the IRB-approved protocol, including consent forms;
- any IRB application forms required by the IRB; and
- any other information requested or required by the IRB to be considered during IRB review.

DHHS-conducted or supported research involving prisoners as subjects may not proceed until OHRP reviews the certification and issues its authorization on behalf of the Secretary.

15.6 Research Involving Children and Parental Permission/Assent

The following applies to all research involving children, regardless of funding source. ****no flexibility** The requirements in this section are consistent with Subpart D of 45 CFR 46, which

applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

15.6.1 Allowable Categories

In addition to the IRB's normal duties, non-exempt research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) the category determination must be made for each group assignment. In other words, a component analysis must be conducted by the IRB of record. The categories are as follows:

1. **Research/Clinical Investigations not involving greater than minimal risk** [45 CFR 46.404/21 CFR 50.51]. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 15.6.2.
2. **Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects** [45 CFR 46.405/21 CFR 50.52]. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents that:
    a. The risk is justified by the anticipated benefit to the subjects;
    b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
    c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 15.6.2**.**
3. **Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition** [45 CFR 46.406/21 CFR 50.53]. Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents that:
    a. The risk represents a minor increase over minimal risk;

b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

d. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 15.6.2.

4. **Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children** [45 CFR 46.407/21 CFR 50.54]. When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, the IRB shall refer the research for further review as follows:

    a. DHHS-conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must determine that the proposed research also meets all of the requirements of the Common Rule.

    b. FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.

    c. For research that is not DHHS conducted or supported and not FDA-regulated, the IRB of record will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:

        i. That the research in fact satisfies the conditions of the previous categories, as applicable; or

        ii. The following:

            1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

            2. The research will be conducted in accord with sound ethical principles; and

            3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 15.6.2.

    d. If the IRB of record approves research not otherwise approvable, the CW HRPP must be involved in the final review and agree to the research being conducted

in CW. Documentation from the Institutional Official must be on file prior to implementation of the research.

15.6.2 Parental Permission and Assent

15.6.2.1 Parental Permission

The IRB of record must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB of record deems necessary, as described in Section 14.

The IRB of record may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless:

1. One parent is deceased, unknown, incompetent, or not reasonably available; or
2. When only one parent has legal responsibility for the care and custody of the child.

The IRB of record may waive the requirement for obtaining permission from a parent or legal guardian if:

1. The research meets the provisions for waiver in Section 14.10; or
2. For research that is not FDA-regulated, if the IRB determines that the research is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 14.7.

15.6.2.2 Assent from Children

The IRB of record is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate. In the course of determining acceptability of the

assent process, it is CW HRPP expectation that the IRB of record will take into consideration local context practice that will be addressed in CW guidance to be published and updated from time to time as well as this SOP manual.

If the IRB of record determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for research that meets the provisions for a general waiver in Section 14.10.

Because "assent" means a child's affirmative agreement to participate in research, the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way.

The IRB of record should take into account the nature of the proposed research activity and the ages, maturity, and psychological state of the children involved when reviewing the proposed assent procedure and the form and content of the information conveyed to the prospective subjects. For research activities involving adolescents whose capacity to understand resembles that of adults, the assent procedure should likewise include information similar to what would be provided for informed consent by adults or for parental permission. For children whose age and maturity level limits their ability to fully comprehend the nature of the research activity, but who are still capable of being consulted about participation in research, it may be appropriate to focus on conveying an accurate picture of what the actual experience of participation in research is likely to be (for example, what the experience will be, how long it will take, whether it might involve any pain or discomfort). The assent procedure should reflect a reasonable effort to enable the child to understand, to the degree they are capable, what their participation in research would involve. This is a study-specific assessment and does not have specific age ranges defining when assent would or would not be required.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

Documentation of Assent

When the IRB determines that assent is required, it also is also responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures and/or other mediums (video, cartoons, graphic novels, etc.) with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide

the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and form that is age appropriate and study specific, taking into account the typical child's experience and level of understanding, and composing a document that treats the child respectfully and conveys the essential information about the study. The assent form should:

1. Tell why the research is being conducted;
2. Describe what will happen and for how long or how often;
3. Say it is up to the child whether to participate and that it is okay to say no;
4. Explain if it will hurt and if so for how long and how often;
5. Say what the child's other choices are;
6. Describe any good things that might happen;
7. Say whether there is any compensation for participating; and
8. Ask for questions.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age-appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language. When deemed appropriate, the Parental Permission form can be used to document the assent process provided the information was presented via a mechanism understandable to the potential subject. Additional suggestions can be found on the CW HRPP web pages.

15.6.2.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 15.6.1), **only if such research** is:

1. Related to their status as wards; or
2. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

If the research meets the condition(s) above, an advocate must be appointed for each child who is a ward (one individual may serve as advocate for more than one child), in addition to any other individual acting on behalf of the child as legal guardian or in *loco parentis.*

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Note: In Wisconsin, the term Ward is also used when an individual has a court-appointed legal guardian. Due to the variable nature of guardianship rights, legal and the CW HRPP should be consulted on a case-by-case basis.

15.7 Adults with Impaired Decision-Making Capacity

When vulnerable populations are included in research, regulations require that additional safeguards are put in place to protect the rights and welfare of these subjects. [45 CFR 46.111(b)/21 CFR 56.111(b)] Adults who lack or who have impaired, fluctuating, or diminishing decision-making capacity (collectively referred to as "adults with impaired decision-making capacity" in this section) are particularly vulnerable. Investigators and IRBs must carefully consider whether inclusion of such subjects in a research study is appropriate; and when it is, must consider how best to ensure that these subjects are adequately protected. The principals and procedures outlined in this section are intended to assist Children's Wisconsin investigators and the IRB with the development and review of research involving adults with impaired decision-making capacity.

15.7.1 Informed Consent

Obtaining legally effective informed consent before involving human subjects in research is one of the central ethical principles described in the Belmont Report and provided for by federal regulations governing research.

As discussed previously, the informed consent process involves three key features: (1) providing the prospective subject the information needed to make an informed decision (in language understandable to him or her); (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Among other requirements, for consent to be legally effective, the potential subject or their LAR must have the necessary decision-making capacity to make a rational and meaningful choice about whether to participate (or continue participating) in a study.

15.7.2 Decision-Making Capacity

"Decision-making capacity" refers to a potential subject's ability to make a rationale and meaningful decision about whether or not to participate in a research study. This ability is generally thought to include at least the following four elements:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, the risks and benefits of participating versus not participating, and the voluntary nature of participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one's own situation and condition;

3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives, and;
4. Choice, i.e., the ability to express a choice about whether or not to participate.

"Decision-making capacity" should not be confused with the legal concept of "competence." While the court may consider information about a person's decision-making capacity in making a competency determination, the terms are not synonymous. Incompetence is a legal determination made by a court of law. For example, someone who is judged legally incompetent to manage their financial affairs may retain sufficient decision- making capacity to make meaningful decisions about participating in a research protocol. Likewise, people who have normal cognitive functioning and are considered legally competent may be put into circumstances where their decision-making capacity is temporarily impaired by a physical or mental condition or by alcohol or drugs.

Decision-making capacity is protocol and situation specific. A person may have capacity to consent to participate in low-risk research in usual circumstances, but not have the capacity to consent to a higher risk protocol when s/he is under significant stress or faced with unfamiliar circumstances.

15.7.3 Inclusion of Adults with Impaired Decision-Making Capacity in Research

Research involving adult subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation.

Investigators must disclose to the IRB both plans and justification for including adults with impaired decision-making capacity in a given research proposal. If adults with questionable or fluctuating capacity will be included, investigators must specify procedures for assessing capacity prior to providing informed consent and, if appropriate, for re-evaluating capacity during study participation. If a prospective subject's capacity to consent is expected to diminish, the investigator should consider requesting that the subject designate a future LAR prior to enrollment in the research, including the future LAR in the initial consent process, and obtaining written documentation of the subject's wishes regarding participation in the research. When the study includes subjects likely to regain capacity to consent while the research is ongoing, the investigator should include provisions to inform them of their participation and seek consent for ongoing participation.

Plans for evaluation of capacity should be tailored to the subject population and the risks and nature of the research. In some instances, assessment by a qualified investigator may be appropriate. However, an independent, qualified assessor should evaluate subjects' capacity when the risks of the research are more than a minor increase over minimal or the investigator is in a position of authority over a prospective subject. In all cases, the person(s) evaluating capacity must be qualified to do so and use appropriate, validated tools and methods (e.g., University of California, San Diego Brief Assessment of Capacity to Consent [UBACC], MacArthur

Competence Assessment Tool for Clinical Research [MacCAT-CR]). Assessments of capacity should be documented in the research record, and when appropriate, in the medical record.

Under some circumstances, it may be possible for investigators to enable adults with a degree of decisional impairment to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, audiovisual presentations, and oral or written recall tests. Other measures might include follow-up questions to assess subject understanding, videotaping or audiotaping of consent discussions, use of waiting periods to allow more time for the potential subject to consider the information that has been presented, or involvement of a trusted family member or friend in the disclosure and decision-making process. Audio or videotapes, electronic presentations, or written materials used to promote understanding must be provided to the IRB for review and approval prior to use.

When a prospective subject is deemed to lack capacity to consent to participate in research, investigators may obtain informed consent from the individuals' surrogate or LAR (See Section 14.2). Under these circumstances, the prospective subject should still be informed about the research in a manner compatible with the subjects' likely understanding and, if possible, be asked to assent to participate. Potential subjects who express resistance or dissent (by word, gesture, or action) to either participation or use of surrogate consent, should be excluded from the study. Some subjects may initially assent but later resist participation. Under no circumstances may an investigator or caregiver override a subject's dissent or resistance. When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, how assent will be documented, and a copy of the assent form. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB.

When inclusion of adults with impaired decision-making capacity is **not anticipated** and a plan for inclusion of such subjects **has not been** reviewed and approved by the IRB, and an enrolled subject becomes unable to provide consent or impaired in decision-making capacity, the investigator is responsible for promptly notifying the IRB (as soon as possible but within 5 business days). The investigator should consider whether continuing participation is appropriate and, if so, present a plan for surrogate consent from a LAR and, if appropriate, a plan to periodically evaluate capacity and re-obtain consent if possible.

15.7.4 IRB Review

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

15.8 Other Vulnerable Populations – RESERVED

Children's Wisconsin does not currently review on a regular basis research involving other vulnerable populations such as, research involving economically or educationally disadvantaged persons, employees, students, refugees, undocumented workers, mental health patients under involuntary holds, etc.).

16 FDA-Regulated Research

FDA regulations apply to research that involves an FDA-regulated *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If the research is conducted or supported by a Common Rule agency or department, or if compliance with the Common Rule is required by state law, or the terms of an FWA, IAA, or an award or contract, then the Common Rule must also be applied.

Clinical investigations of investigational drugs and biological products must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Evaluations of the safety or effectiveness of a medical device must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research by the Children's Wisconsin HRPP.

Also, refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

16.1 Definitions

Bioavailability. Bioavailability (BA) is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action. Bioavailability studies, including determining when an IND is required, are regulated under 21 CFR 320.

Bioequivalence. Bioequivalence (BE) is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be assessed by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action. Bioequivalence studies, including determining when an IND is required, are regulated under 21 CFR 320.

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Clinical Investigation. Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [21 CFR 50.3(c)]

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. [21 U.S.C. 321(ff)]

Emergency Use. Emergency use is defined as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [21 CFR 56.102(d)]

Emergency Use Authorization. FDA's Emergency Use Authorization (EUA) authority is intended to help strengthen the nation's public health protections against chemical, biological, radiological, and nuclear (CBRN) threats, including infectious diseases, by facilitating the availability and use of medical countermeasures (MCMs) needed during public health emergencies. Under the FD&C Act), when the DHHS Secretary declares that an EUA is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when certain criteria are met. Products authorized under an EUA are not subject to IRB oversight.

Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/P's) – HCT/P's means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.

The following articles are not considered HCT/P's: vascularized human organs for transplantation; whole blood or blood components or blood derivative products subject to listing under parts 607 and 207, respectively; secreted or extracted human products, such as

milk, collagen, and cell factors; except that semen is considered an HCT/P; minimally manipulated bone marrow for homologous use and not combined with another article (except for water, crystalloids, or a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow); ancillary products used in the manufacture of HCT/P; cells, tissues, and organs derived from animals other than humans; in vitro diagnostic products as defined in 809.3(a); blood vessels recovered with an organ, as defined in 42 CFR 121.2, that are intended for use in organ transplantation and labeled "For use in organ transplantation only."

HCT/P's may be regulated as drugs, devices, and/or biologics when the use does not qualify for an establishment exception or regulation solely under section 361 of the PHS Act and 21 CFR 1271.

Humanitarian Use Device (HUD). A Humanitarian Use Device is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

Investigational Drug. Investigational *or* experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

IND. IND means an investigational new drug application in accordance with 21 CFR Part 312.

IDE. IDE means an investigational device exemption in accordance with 21 CFR 812.

In Vitro Diagnostic Product (IVD). In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the FD&C Act, and may also be biological products subject to section 351 of the PHS Act, including when the manufacturer of these products is a laboratory. [21 CFR 809.3(a)]

Non-Significant Risk (NSR) Device. A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

Significant Risk (SR) Device. Significant risk device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. [21 CFR 812.3(m)]

16.2 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

16.3 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical investigation subject to FDA regulations. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.
2. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the FDA or IRB.
3. The investigator is responsible for personally conducting or supervising the investigation. When study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
4. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training

conducted by the investigator or sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

5. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
    a. Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
    b. Providing or arranging for reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
    c. Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
    d. Adhering to the protocol so that study subjects are not exposed to unreasonable risks
    e. As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.
6. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
7. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include but are not limited to correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such. For clinical investigations of medical devices, required records must be maintained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
8. The investigator is responsible for controlling test articles according to FDA regulations and the Controlled Substances Act, if applicable.

9. For research reviewed by the Children's Wisconsin HRPP and the IRB of record, the investigator proposing the clinical investigation will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the test article.
    a. The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB for acceptability.
    b. The investigator may delegate in writing, as part of the IRB submission, the responsibility detailed in 'a' above to the Pharmacy Service.
    c. Investigational drugs and devices must be labeled in accordance with federal and state standards.
    d. All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device, and the disposition of remaining devices at the conclusion of the investigation.
10. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
11. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

16.4 Digital Health

Certain medical and decision support software have been excluded from the definition of medical device under the 21st Century Cures Act and thus are not subject to FDA's regulations. These include exclusions for software functions:

- Intended for administrative support of a health care facility, including the processing and maintenance of financial records, claims or billing information, appointment schedules, business analytics, information about patient populations, admissions, practice and inventory management, analysis of historical claims data to predict future utilization or cost-effectiveness, determination of health benefit eligibility, population health management, and laboratory workflow;
- Intended for maintaining or encouraging a healthy lifestyle and unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition;
- Intended to serve as electronic patient records, including patient-provided information, to the extent that such records are intended to transfer, store, convert formats, or display the equivalent of a paper medical chart, so long as—

- such records were created, stored, transferred, or reviewed by health care professionals, or by individuals working under supervision of such professionals;
- such records are part of health information technology that is certified under section 300jj–11(c)(5) of title 42; and
- such function is not intended to interpret or analyze patient records, including medical image data, for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition

- Intended for transferring, storing, converting formats, or displaying clinical laboratory test or other device data and results, findings by a health care professional with respect to such data and results, general information about such findings, and general background information about such laboratory test or other device, unless such function is intended to interpret or analyze clinical laboratory test or other device data, results, and findings; and

- Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system; and
  - Is intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);
  - Is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
  - Is intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

Additional information regarding the application of these exclusions is available on the FDA website referenced below.

Research involving software excluded from the definition of medical device will be evaluated by the IRB in accordance with any other applicable regulations (e.g., the Common Rule, HIPAA) and the criteria outlined in this manual.

Other digital health products may be subject to FDA regulations and will be evaluated accordingly. FDA has provided a website listing of Guidances with Digital Health Content to help the regulated community understand FDA's interpretation and application of the regulations and to describe when FDA will practice enforcement discretion in regards to certain requirements such as those for pre-market review and for device reports. Investigators are encouraged to consult these guidances in advance of their submission to the IRB and to consult directly with the FDA as needed.

16.5 Human Cells, Tissues, and Cellular Tissue based Products

Generally, research involving HCT/P's regulated as drugs, devices, and/or biologics will require an IND or IDE depending on how the HCT/P is categorized. Because the regulatory and policy framework for HCT/P's is complex, consultation with the FDA prior to submission to the IRB is encouraged to appropriately categorize the HCT/P, understand which regulations and requirements apply, and to obtain an IND or IDE if necessary (or FDA determination that such is not required).

Contact the HRPP office for assistance and/or to set up a consultation as needed at cwhrpp@childrenswi.org.

16.6 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. Due to a partial stay [80 FR 66907] on FDA's guidance "Investigational New Drug Applications – Determining Whether Human Research Studies Can Be Conducted Without an IND", at this time FDA also does not require an IND for studies intended to evaluate whether a dietary supplement may reduce the risk of a disease or studies intended to support a new or expanded health claim, unless the studies include individuals less than 12 months old, those with altered immune systems, or those with serious or life-threatening medical conditions. All other studies intended to evaluate a dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, require an IND unless FDA grants an exception to the requirement.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans,

documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

16.7 Cannabis and Derivatives

Cannabis and its derivatives, including cannabidiol (CBD), are classified by the FDA as drug products, not as dietary supplements. In most circumstances, research involving the administration of Cannabis and/or its derivatives must be conducted under an IND and comply with FDA's quality requirements. Additional requirements apply when the product is classified as "Marihuana", which is a Schedule 1 controlled substance. Investigators are strongly encouraged to consult with the FDA's Botanical Review Team (BRT) when planning a study involving the use of Cannabis and/or its derivatives to ensure that the study conforms with regulatory requirements and avoid delays in Children's Wisconsin HRRP and IRB review and approval of the research. Investigators are also encouraged to review the information on FDA's website: FDA and Cannabis: Research and Drug Approval Process.

16.8 Clinical Investigations of Articles Regulated as Drugs or Devices

16.8.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug or device under FDA regulations, the investigator must indicate on the IRB application whether an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the sponsor or the sponsor-investigator. Contact the HRPP office for assistance and/or to set up a consultation as needed at cwhrpp@childrenswi.org.

Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

1. Industry sponsored study with IND/IDE number indicated on the protocol;
2. Letter/communication from FDA;
3. Letter/communication from industry sponsor; or
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements (IDE-exempt) or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as IDE-exempt or NSR, then the investigator should include documentation with the submission providing the basis for IDE-exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the study is IDE-exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine:

1. That there is an approved IND/IDE in place;
2. That the FDA has determined that an IND is not required or that a device study is IDE-exempt or NSR; or,
3. If neither of the above, whether an IND is necessary, or that a device study is exempt or NSR, or whether the study must be submitted to the FDA, using the criteria below.

The IRB cannot grant approval to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place.

16.8.2 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. 21 CFR 312.2(b)(1): The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
    a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
    b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
    c. The research does not involve a route of administration, dose, subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
    d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
    e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
    f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

    Please Note: FDA has provided specific guidance for evaluating whether this exemption applies to studies of marketed drugs/biologics for the treatment of cancer.
2. 21 CFR 312.2(b)(2): For clinical investigations involving defined (blood grouping serum, reagent red blood cells, and anti-human globulin) in vitro diagnostic biological products, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160

3. 21 CFR 312.2(b)(5): A clinical investigation involving use of a placebo is exempt from the requirements of part 312 if the investigation does not otherwise require submission of an IND.
4. 21 CFR 320.31(b) and (d): Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
    a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
    b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
    c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
    d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].
5. 21 CFR 361.1: Research using a radioactive drug or biological product if all of the following conditions are met:
    a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
    b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
    c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
    d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
6. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
    a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
    b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
    c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
    d. The quality of the cold isotope meets relevant quality standards; and

e. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts 56 and 50, respectively]

16.8.3 IDE Exemptions

For clinical investigations of medical devices, an IDE is not necessary if:

1. The research involves a device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;
2. The research involves a device other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of 21 CFR 807 in determining substantial equivalence (a "510k" device);
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and if the testing:
    a. Is noninvasive,
    b. Does not require an invasive sampling procedure that presents significant risk,
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;
4. The research involves a device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
5. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. The research involves a custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

16.8.4 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in Section 16.8.1. The FDA's determination is final, and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to the sponsor or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
    a. Labels the device in accordance with 812.5;

b. Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;

c. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless the requirement is waived by the IRB;

d. Complies with the requirements of 812.46 with respect to monitoring investigations;

e. Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

f. Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

g. Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

16.9 Diagnostic or Treatment Use of Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that an IRB (or alternate institutional committee) approve the use of a HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

Additional information can be found in the HUD article on the HRPP pages on the CW Connect intranet

16.9.1 Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a "premarket approval application" submitted to FDA pursuant to Subpart A, 21 CFR Part 814 "seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act]." HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person or entity that obtains approval of an HDE from the FDA.

16.9.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB (or alternative institutional committee) has approved its use, except in certain emergencies.

When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for an FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

16.9.3 Procedures

The relevant requirements and procedures for research described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at Children's Wisconsin facilities is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, organizational policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. Application Form – Humanitarian Use Devices (non-research uses);
2. A copy of the HDE approval letter from the FDA;
3. A description of the device, such as a device brochure;
4. The product labeling;
5. The patient information packet for the HUD;
6. The proposed clinical consent process (note: CW HRPP requires prospective written consent for HUDs when consent is possible; the HUD user can request an alteration with justification specific to the circumstances of device use); and
7. Other relevant materials (e.g., training certificates) as identified in the Application Form.

The IRB will review the proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants. The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB of record will

evaluate the patient information packet and proposed consent document and process and will determine if the materials are adequate and appropriate for the patient population and are consistent with CW's policy and expectation for informed consent.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. Proposed changes may be submitted using the Amendment Form and should be accompanied by any revised materials or supporting documentation. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date, in accordance with CR submissions policy in this manual to ensure IRB review and re-approval prior to expiration. Submission for continuing review MUST be submitted no later than 60 days before the date of expiration. Materials to be submitted include:

1. The Continuing Review Report – Humanitarian Use Devices (non-research uses)
2. The most recent periodic report to the FDA by the HDE holder;
3. The current patient information packet, if applicable;
4. The current consent, if applicable;
5. Other materials as identified on the Continuing Review Report; and
6. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

16.9.4 Emergency Uses of HUDs

Unapproved HUDs - If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The provider must comply with the HDE holder's requirements for certification of the emergent need for the HUD. Within 5 days after the emergency use of the device, the provider must provide written notification of the use to the Children's Wisconsin HRRP and the IRB Chair including the identification of the patient involved, the date of the use, and the reason for the use. [21 CFR 812.124] This notification should be submitted via the IRB electronic submission platform.

Off-label Use of HUDs - If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indications, the physician should consult with the HDE holder and IRB in advance whenever possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The CW HRPP or the IRB of record may require additional reports, patient protection measures, or other requirements, as appropriate given the specifics of the situation.

16.10 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as "compassionate use", are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to the use of investigational or unapproved/uncleared medical products (all referred to as "investigational" throughout this section) outside of a clinical trial, where the primary intent is treatment, rather than research. Because the products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their LAR and to monitor for safety.

Charging for expanded access use of investigational products is discussed in Section 16.11.

For references to IRB review in this section, CW HRPP primarily relies on the review of the MCW pediatric IRBs; however, review may be delegated to another external IRB when appropriate.

16.10.1 Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs for patients with serious or immediately

life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational agent. Expanded access is sometimes referred to as compassionate use or treatment use.

For the purposes of expanded access to investigational drugs, ***immediately life-threatening disease or condition*** means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. ***Serious disease or condition*** means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. [21 CFR 312.300(b)]

Expanded access may also apply to (1) situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS); and (4) use for other reasons. All are referred to as "investigational" for the purposes of these SOPs.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes is available to:

- Individual patients, including in emergencies [21 CFR 312.310]
- Intermediate-size patient populations [21 CFR 312.315]
- Widespread use under a treatment protocol or treatment IND [21 CFR 312.320]

The following section addresses expanded access for individual patients. Investigators seeking expanded access for intermediate-size populations or widespread use should review the *Expanded Access Information Sheet* (link forthcoming) and consult with the CW HRPP office as needed. Convened IRB review is required for intermediate or widespread expanded access unless the FDA has issued a waiver.

Physicians seeking access to investigational drugs under expanded access should work closely with the sponsor or manufacturer, the FDA, and the Children's Wisconsin HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed. The FDA provides information about the procedures and requirements for expanded access on a website, including a link to FDA's contact information.

16.10.1.1 Expanded Access to Investigational Drugs for Individual Patients

Expanded access to investigational drugs may be sought under an "Access Protocol" or an "Access IND". FDA generally encourages Access Protocols, which are managed and submitted by the sponsor of an existing IND, because it facilitates the review of safety and other

information. However, Access INDs for the treatment of individual patients are also available and commonly used when: (1) a sponsor holding an existing IND declines to be the sponsor for the individual patient use (e.g., because they prefer that the physician take on the role of sponsor-investigator); or (2) there is no existing IND.

Sponsor or Manufacturer Approval:

Prior to submitting to the FDA or IRB, physicians seeking expanded access to an investigational drug should contact the sponsor (e.g., for investigational drugs under a commercial IND) or manufacturer (e.g., for approved drugs under a REMS) to: (1) ensure that the investigational drug can be obtained; (2) determine whether the patient may be treated under an existing IND study, sponsor-held Access Protocol, or if the physician should seek an Access IND; and (3) determine if the drug will be provided free or if there will be a charge. A Letter of Authorization (LOA) from the sponsor or manufacturer should be obtained.

FDA Approval:

When a commercial sponsor agrees to provide access under an Access Protocol, the sponsor is responsible for managing and obtaining FDA approval and all other sponsor responsibilities. A licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access is considered an "investigator" under FDA regulations and is responsible for all investigator responsibilities under 21 CFR 312, to the extent they are applicable to expanded access.

If the sponsor or manufacturer declines treatment of the patient under an existing IND study or Access Protocol but agrees to make the investigational drug available for the patient, physicians may apply to the FDA for an individual patient Access IND using Form FDA 3926, a streamlined IND application specifically designed for such requests. Form FDA 3926, and related guidance, is available on a FDA website. Form FDA 3926 includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a "concurrence review" in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review can also be used for any post-approval reviews (e.g., unanticipated problems, continuing review, closure, etc.).

When there is an emergency situation and insufficient time to submit a written application to the FDA prior to treatment, a request to FDA for emergency use may be made by telephone (or other rapid means). A written expanded access application must be submitted within 15 days of the FDA's authorization. For more information on emergency use, see Sections 16.10.1.2, 16.10.1.3.

A physician who obtains an Access IND is considered a "sponsor-investigator" and is responsible for the responsibilities of both sponsors and investigators under 21 CFR 312, as applicable, including IND safety reports, annual reports, and maintenance of adequate drug accountability records.

For additional CW requirements related to this these requests, refer to the the CW HRRP Guidance Individual Patient Expanded Access (IND) Applications.

IRB Review:

Unless the conditions that permit an emergency use exemption (see Section 16.10.1.2.1) are satisfied, IRB approval must be obtained prior to initiating treatment with the investigational drug. When the FDA has authorized the use of alternative IRB review procedures (which can be presumed when the request is made on Form FDA 3926 unless the FDA specifically states that the request is denied), the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using investigational drugs under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the drug and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the drug.

To request IRB approval for single patient expanded access, investigators should refer to the the CW HRRP Guidance Individual Patient Expanded Access (IND) Applications, contact the HRPP office and submit the documents as indicated in this guidance via the IRB electronic system.

The IRB may review the expanded access application prior to FDA approval being received but cannot finalize approval until documentation of FDA approval is provided. The IRB will provide the investigator with written documentation of its review.

Children's Wisconsin may consider on a case by case basis, reliance upon an external IRB for expanded access when the IND is held by a commercial sponsor and an external IRB has approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the HRPP office to discuss IRB reliance for expanded access protocols.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, copies of any follow-up submissions to the FDA related to the expanded access use must be submitted to the IRB within 7 business days of the date of submission to the FDA.

16.10.1.2 Emergency Use of Investigational Drugs

FDA regulations permit the use of an investigational drug without IRB approval when an appropriately trained and licensed health care provider determines that IRB approval for the

use of the drug cannot be obtained in time to prevent serious harm or death to a patient. The provider is expected to assess the potential for benefit from the use of the drug and to have substantial reason to believe that benefits will exist. The criteria and requirements for this Emergency Use Exemption are explained in Section 16.10.1.2.1 below.

Approval from the FDA and the Sponsor/Manufacturer must be obtained prior to initiating treatment with the drug.

Providers invoking the emergency use exemption must comply with any applicable FDA follow-up requirements including submission of safety reports, amendments, a summary following completion of treatment, and annual reports.

A copy of reports or amendments submitted to the FDA and any related correspondence must be submitted to the IRB of record office.

Note: DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46. However, nothing in the DHHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state or local law.

16.10.1.2.1 Emergency Use Exemption from Prospective IRB Approval

Under FDA regulations at 21 CFR 56.104(c), FDA exempts the emergency use of an investigational drug (or biologic classified as a drug) from the requirement for prospective IRB approval, provided that the conditions described below are satisfied and that the emergency use is reported to the IRB within 5 working days. Any subsequent use of the investigational drug in the facility requires IRB approval. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. If it appears likely that the investigational drug may need to be used again, the IRB may request that a study application is submitted which would cover future uses.

FDA defines emergency use as the use of a test article in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist, then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating.

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-

threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 16.10.1.3), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within **5 working days** after an emergency exemption is used The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as IRB approval, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB prior to the emergency use, the IRB Chair or designee will review the proposed use, and, if appropriate, provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Reports of emergency uses will be brought to the convened IRB for their information.

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved drugs.

16.10.1.3 Emergency Exception from the Informed Consent Requirement (single patient)

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational drug without informed consent when the investigator and an independent physician who is not otherwise participating in the clinical investigation (the emergency use) certify in writing all four of the following conditions:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article;
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
3. Time is not sufficient to obtain consent from the subject's LAR; and
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within **5 working days** when an emergency consent exception is invoked via the electronic submission system. See Children's Wisconsin guidance on Connect

intranet Treatment Use (Expanded Access) of Investigational Drugs/Biologics – Individual Patient – Treated at Children's Wisconsin for details.The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

16.10.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use

Investigators seeking access to investigational or unapproved devices under one of the above provisions should work closely with the sponsor or manufacturer, the FDA, and the Children's Wisconsin HRPP, to ensure that proper regulatory procedures are followed.

FDA has made information about expanded access to medical devices available on a website.

For additional CW requirements related to this these requests, refer to CW HRRP Guidance: guidance Individual Patient Expanded Access (IDE) Applications.

16.10.2.1 Compassionate Use of Investigational/Unapproved Medical Devices

The compassionate use provision under expanded access provides a mechanism for accessing investigational devices for an individual patient or small groups of patients when the treating physician believes the device may provide a diagnostic or treatment benefit. Compassionate use can be used for devices being studied in a clinical trial under an IDE for patients who do not qualify for inclusion in the trial, and for devices for which an IDE does not exist. The following criteria must be satisfied:

1. The patient has a life-threatening or serious disease or condition; and
2. No generally acceptable alternative treatment for the condition exists.

The medical device company must agree to make the medical device available for the proposed compassionate use. FDA and IRB approval are required before the device may be used under the compassionate use provision.

FDA Approval:

When **there is an IDE** for the device, the IDE sponsor submits an IDE supplement requesting approval for the compassionate use under 21 CFR 812.35(a).

When **there is not an IDE** for the device, the physician or manufacturer submits the following information to the FDA:

1. A description of the device (provided by the manufacturer);
2. Authorization from the device manufacturer for the use;
3. A description of the patient's condition and the circumstances necessitating treatment or diagnostics (when seeking small group access, the number of patients to be treated;
4. A discussion of why alternative therapies/diagnostics are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition; and
5. The patient protection measures that will be followed, including:
    a. A draft of the informed consent document that will be used;
    b. Clearance from the institution as specified by their policies (see below);
    c. Concurrence (approval) of the IRB Chair or Chair-designated IRB member (prior to FDA request when possible); and
    d. An independent assessment from an uninvolved physician.

When IRB Chair approval cannot be obtained in advance of the submission to the FDA, the request should indicate that approval from the IRB Chair will be obtained prior to use of the device. Proof of IRB Chair approval must be submitted with the follow-up report to the FDA after the patient is treated (or the diagnostic is used).

When the compassionate use is conducted under an IDE, a licensed provider who receives an investigational device is an "investigator" under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under 21 CFR 812 (IDE regulations), 21 CFR 50 (Informed Consent), and 21 CFR 56 (IRB).

When the provider obtains an IDE for compassionate use, the provider is considered a "sponsor-investigator" and is responsible for the responsibilities of both sponsors and investigators under 21 CFR 812, as applicable, including medical device reports and progress reports .

IRB Review:

Unless the conditions that permit an emergency use exemption are satisfied (see Section 16.10.2.3), IRB approval must be obtained prior to initiating treatment with the investigational device. When the request is for single-patient compassionate use, the review may be conducted by the IRB of record Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using medical devices under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the device and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the device.

To request IRB approval for compassionate use, investigators should contact the CW HRPP office for guidance. For additional CW requirements related to this these requests, refer to CW HRRP guidance Individual Patient Expanded Access (IDE) Applications.

The IRB of record may review the expanded access application prior to FDA approval being received but may condition approval upon receipt of FDA approval. The IRB will provide the investigator with written documentation of its review.

Children's Wisconsin may consider reliance upon an external IRB for Compassionate Use protocols on a case-by-case basis when the IDE is held by a commercial sponsor and an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the CW HRPP office, to discuss reliance for Compassionate Use protocols.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, a follow-up report to the FDA is required following a compassionate use by whomever submitted the original request to the FDA. The report should include summary information regarding patient outcome and any problems that occurred as a result of the device. A copy of the follow-up report to the FDA and any other post-approval submissions or reports to the FDA must be submitted to the IRB within 7 business days of the date of submission to the FDA, and will be reviewed by the CW HRPP.

16.10.2.2 Treatment Use of Investigational/Unapproved Medical Devices

During the course of a clinical trial under an IDE, if the data suggest that the device under study is effective, the trial may be expanded to include additional patients with life-threatening or serious diseases under the Treatment Use provision for expanded access. "Treatment Use" also applies to the use of a device for diagnostic purposes under these same conditions. [21 CFR 812.36]

The following criteria must be satisfied for Treatment Use to apply:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;

2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

The IDE sponsor is responsible for applying for a Treatment Use IDE.

A licensed provider who receives an investigational device for treatment use under a Treatment Use IDE is an "investigator" under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under 21 CFR 812 (IDE regulations), 21 CFR 50 (Informed Consent), and 21 CFR 56 (IRB).

IRB Review:

IRB approval is required before the investigational device/diagnostic is used.

Children's Wisconsin will consider reliance upon an external IRB for Treatment Use IDE protocols on a case-by-case basis when an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the CW HRPP office, to discuss IRB reliance for Treatment Use IDEs.

Post-Approval Requirements

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), for reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, the semi-annual (applicable until the marketing application is filed) or annual (applicable after the marketing application is filed) progress report from the sponsor must be submitted to the IRB within 7 business days of receipt.

16.10.2.3 Emergency Use of Investigational Devices

FDA regulations permit the emergency use of an investigational or unapproved device without prior approval by the FDA or IRB when an appropriately trained and licensed health care provider determines that:

- The patient has a life-threatening or serious disease or condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

FDA expects the provider to make the determination that the above criteria are satisfied, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. Because prior FDA approval is not required, FDA expects providers planning the emergency use of an investigational device to obtain as many of the following as possible:

- An independent assessment from an uninvolved physician;
- Authorization from the device manufacturer;
- Concurrence of the IRB Chair or designee;
- Institutional clearance; and
- Informed consent from the patient or legally authorized representative.

At Children's Wisconsin, providers planning the emergency use of an investigational or unapproved device must contact the HRPP office as early in the process as possible and submit, via the electronic submission system, supporting documentation called for in the Children's Wisconsin HRRP guidance Individual Patient Expanded Access (IDE) Applications for review by the IRB Chair or designee. The IRB Chair or designee will review the information provided and determine whether the use conforms with FDA's requirements and expectations and whether the provisions for the protection of the patient appear adequate using the applicable criteria at 21 CFR 50 and 56 as guidelines (e.g., minimization of risks, risk/benefit, safety monitoring, informed consent, etc.).

Note: If the device comes from another institution (for example Froedtert Hospital), the supplying institution must also be notified of this emergency use.

The emergency use must be reported to the FDA by the IDE Sponsor, when one exists, or by the provider if no IDE exists. Information regarding what to include in the report and where to submit it is available on FDA's website. When the provider is responsible for the FDA report, a copy of the report and any related correspondence must be submitted to the CW HRPP and the IRB office.

Reports of emergency uses will be brought to the convened IRB for their information.

Providers are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved devices.

16.11 Charging Subjects for Investigational Products

FDA regulations do not prohibit charging subjects or their insurers for investigational products so long as those charges comply with specified criteria. FDA approval of such charges does not obviate the investigator's and IRB's responsibility to minimize risks to subjects (Beneficence), to ensure that the risks and burdens associated with research are equitably distributed (Justice), and to ensure that subjects are properly informed and not unduly influenced to accept an otherwise unacceptable risk or cost in order to access a benefit (Respect for Persons). Any

costs to subjects or insurers must be described in the IRB application and informed consent document.

16.11.1 Charging for Investigational Medical Devices and Radiological Health Products

IDE regulations allow sponsors to charge for an investigational device, however, the charge may not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.7(b)]. Sponsors must justify the proposed charges for the device in the IDE application, state the amount to be charged, and explain why the charge does not constitute commercialization [21 CFR 812.20(b)(8)].

16.11.2 Charging for Investigational Drugs and Biologics

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs Under an IDE. These rules:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug for an expanded access for treatment use [21 CFR 312.8(c)]
- Establish criteria for determining what costs can be recovered when charging for an investigational drug [21 CFR 312.8(d)]

Additional information is available in FDA guidance: Charging for Investigational Drugs Under an IND — Questions and Answers.

17 Unanticipated Problems Involving Risks to Subjects or Others (AAHRPP Domains I and II)

Regulations require an organization to have written procedures for ensuring prompt reporting of "unanticipated problems involving risk to subjects or others" (also referred to as UPs, UAPs, and UPIRTSOs).

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

Refer to Section 6 for additional reporting requirements of Children's Wisconsin HRPP.

17.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UAPs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected; **and**
2. Is at least possibly related to participation in the research; **and**
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized

UAPs also encompass Unanticipated Adverse Device Effects, as defined below, information that sponsors are required to report to the FDA in IND Safety Reports under 21 CFR 312.32 and Serious Adverse Events (SAEs) that occur in Bioavailability (BA) and Bioequivalence (BE) studies.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Serious Unexpected Suspected Adverse Reaction (SUSAR). For research subject to FDA's IND regulations, a Serious Unexpected Suspected Adverse Reaction refers to any suspected adverse reaction to study treatment, including active comparators, that is both serious and unexpected. Sponsors, or sponsor-investigators, are responsible for determining whether an event meets all three components of this definition (i.e., serious & unexpected & suspected adverse reaction), and thus must be reported to the FDA in an IND Safety Report. Investigators are encouraged to consult FDA draft guidance (2021) and final guidance (2012) for information regarding FDA's terminology and its application to safety reporting requirements.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

18 Noncompliance (AAHRPP Domains I and II)

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research being conducted at Children's Wisconsin. Research

under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.2.3.

In conducting its review of protocol deviations, unanticipated problems, subject complaints, and other reportable events, the IRB of record and the CW HRPP will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

18.1 Definitions

Noncompliance is defined as any failure to follow:

- Applicable federal regulations, state or local laws, or institutional policies governing human subject protections, or
- The requirements of the CW HRPP, requirements or determinations of the IRB of record, including the requirements of the approved investigational plan (i.e., protocol deviations).

Noncompliance can result from performing an act that violates these requirements or failing to act when required. Noncompliance may be minor or sporadic or it may be serious or continuing.

Serious Noncompliance is defined as noncompliance that increases risk of harm to subjects; adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data or the research.

Continuing Noncompliance is defined as a pattern of repeated noncompliance which continues after it has been determined that noncompliance occurred, including inadequate effort to take corrective actions or comply with IRB requirements within a reasonable timeframe.

Apparent Noncompliance describes an event that appears to constitute noncompliance, but the IRB of record has not yet made a formal assessment of the event.

18.2 Reporting

Investigators and their study staff are required to report instances of possible noncompliance in accordance with the policies of the IRB of record. Additionally, anyone may report concerns of possible noncompliance to the CW HRPP or IRB verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the CW HRPP office directly to discuss the situation informally.

18.3 Review Procedures

Please see the applicable policies and procedures of the IRB of record.

When MCW pediatric IRB is the IRB of record:

- The CW HRPP will concurrently review the submission in the electronic submission system. The CW HRPP may have additional questions and/or requirements which will be communicated via the electronic submission system.

When another IRB is the IRB of record:

- The CW HRPP will review the materials submitted to the IRB of record. A copy of these materials must be submitted to the CW HRRP via the local electronic submission system following submission to the IRB of record. The CW HRPP may have additional questions and/or requirements which will be communicated via the electronic submission system.
- The CW HRPP also requires the final determination of the IRB of record which must be submitted as a follow-up report via the local electronic submission system.

18.4 Apparent IRB Noncompliance

When there has been apparent serious or continuing noncompliance on the part of the IRB of record (e.g., repeated failure to make a required determination), the CW HRPP will gather the relevant facts and report the matter, with any recommendations, to the IO. The IO may take actions as needed to further investigate the matter (e.g., a directed audit) prior to determining whether the apparent noncompliance is serious or continuing. The IO may also require corrective and preventive actions as warranted to remedy the matter and prevent recurrence. Serious or continuing noncompliance on the part of the IRB of record will be reported as necessary following the procedures outlined in Section 21.

19 Complaints

The HRPP will be responsive and sensitive to the complaints or concerns expressed by subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, they will try to resolve them.

Investigators conducting research under the auspices of Children's Wisconsin must report complaints to the Children's Wisconsin HRPP regardless of who serves as the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.2. Investigators are encouraged to contact the RIM when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP office is the direct recipient of complaints or concerns, the staff will do the following:

1. Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.

2. Reassure the subject that the HRPP will take all necessary measures to inquire into the circumstances and to address the issue.
3. Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
4. Convey the information to the IRB of record in a timely manner.
5. When appropriate, contact the investigator for additional information or to assist with resolution.
6. When appropriate, contact other resources (e.g., CW Research Compliance/Privacy Officer, CW Risk Management, CW Patient Relations, MCW HRPP, etc.) to assist with information-gathering or resolution.

The HRPP will maintain written copies of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP receives a complaint, or identifies information while investigating a complaint, that is indicative of possible misconduct in research, Research Integrity Officer (or designee) will be notified immediately.

20 Other Reportable Information (AAHRPP Domains I and II)

Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 6.2.

20.1 Review Procedures

1. Upon receipt of the report, the HRPP staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the information provided suggests that Children's subjects may be at risk of harm without immediate intervention or that research misconduct may have occurred, the RIM and, when appropriate, the IO (or designee), will be notified so that they can take any necessary steps to ensure the safety of subjects or investigate the matter.

2. If the reviewer determines that there is additional reporting or action required, HRPP staff will work with the IRB of record to ensure this is addressed appropriately.

21 Reporting to Federal Agencies, Departments, and Organizational Officials (AAHRPP Domains I and II)

Federal regulations require prompt reporting to appropriate institutional officials and, as applicable, the federal department or agency (e.g., OHRP, FDA), of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the applicable federal regulations or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. When research is under the oversight of an external IRB, the terms of the agreement with

that IRB will guide reporting. Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

22 Reserved

23 Investigator Responsibilities (AAHRPP Domain III)

Principal Investigators (PIs) are ultimately responsible for the conduct of research. Please refer to the CW policy Research: Conducting Research on Human Subjects at Children's Hospital and Health Systems for more information, including who can serve as PI. PIs may delegate tasks to appropriately trained and qualified members of their research team. However, PIs must maintain oversight and retain ultimate responsibility for the proper conduct of the research.

Within the regulations, the term 'investigator' refers to individuals involved in the design, conduct, or reporting of the research. Such involvement could include one or more of the following:

- Designing the research
- Obtaining information about living individuals by intervening or interacting with them for research purposes
- Obtaining identifiable private information about living individuals for research purposes
- Obtaining the voluntary informed consent of individuals to be subjects in research
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

23.1 Responsibilities

Investigators who conduct research involving human subjects must:

1. Develop and conduct research that is in accordance with the ethical principles in the Belmont Report;
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects;
3. Develop a research plan that ensures the just, fair, and equitable recruitment and selection of subjects;
4. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, include additional safeguards in the study to protect the rights and welfare of these subjects;
5. Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
6. Ensure that there are adequate provisions to protect the privacy interests of subjects;
7. Ensure that there are adequate provisions to protect the confidentiality of data;
8. Have sufficient resources necessary to protect human subjects, including:

a. Access to a population that would allow recruitment of the required number of subjects;

b. Sufficient time to conduct and complete the research;

c. Adequate numbers of qualified staff;

d. Adequate facilities;

e. Necessary equipment;

f. A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability; and

g. When appropriate, a plan to ensure the availability of medical, psychological, or other services that subjects might require as a result of their participation.

9. Ensure that all procedures in a study are performed with the appropriate level of supervision and only by individuals who are licensed or otherwise qualified to perform such under the laws of Wisconsin and the policies of Children's Wisconsin;
10. Ensure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;
11. Ensure that all persons assisting with the research are adequately trained and informed about the protocol and research implementation plan and their specific duties and functions;
12. Promptly report any changes in, addition to, or departure of investigators or research staff to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved);
13. Protect the rights, safety, and welfare of participants;
14. Ensure that when PHI is used, legally effective HIPAA authorization is obtained for each subject unless a Privacy Board or IRB has approved a waiver of the requirement;
15. Ensure that the language in the consent form is consistent with that in the protocol, any associated grant or contract, and, when applicable, the HIPAA authorization;
16. Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their LAR, unless a waiver of the requirement has been approved by the IRB;
17. Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;
18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;
19. Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before the research begins;

20. Ensure that all required reviews and approvals (e.g., COI, IBC, Radiation Safety) are in place before initiating the research;
21. Comply with all IRB decisions, conditions, and requirements;
22. Ensure that studies receive timely continuing IRB review and approval;
23. Report unanticipated problems, deviations, complaints, noncompliance, suspensions, terminations, and any other reportable events to the IRB and the organization, as required by regulations and policy;
24. Notify the IRB if information becomes available that suggests a change to the potential risks, benefits, merit, or feasibility of the research;
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. Seek Children's Wisconsin HRPP assistance when in doubt about whether proposed research requires IRB review;
27. Retain records for the time-period and in the manner described to and approved by the IRB and as required by required by regulations, agreements, and policies;

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described throughout this manual.

23.1.1 Record Retention

Investigator research records, including, but not limited to, signed consent forms and HIPAA authorizations, subject records and data, test article records, IRB records (submission materials, IRB determinations and associated documentation, correspondence to and from the IRB, etc.), and sponsor/grant records must be retained in accordance with regulatory, organizational (Children's Wisconsin), IRB, sponsor or grantor, and journal or publication standards. Records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data. When research is sponsored or grant-supported, consult the contract, grant terms, or other relevant agreements prior to destroying or transferring any records. If there are questions or allegations about the validity of the data or the appropriate conduct of the research, all records must be retained until such questions or allegations have been completely resolved.

The following summarizes a few of the more common regulatory requirements:

1. **OHRP** – research records must be retained for at least 3 years after the completion of the research
2. **HIPAA** – Research authorizations, or documentation of waivers or alterations of authorization, must be held for a minimum of 6 years after the authorization or waiver/alterations was last obtained or in effect, whichever is later
3. **FDA – Drugs** (& biologics classified as drugs) - For a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being

investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified

4. **FDA – Devices** (& biologics classified as devices) - For a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

23.2 Investigator Concerns

Investigators who have concerns or suggestions regarding the conduct of research at CW or with the external IRBs CW relies upon should convey them to the RIM/HRPP office (contact information is available on the HRPP website), Research Compliance Manager, the IO or other responsible parties (e.g., supervisor, Dean, Department Chair), when appropriate. The recipient of the concern will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted.

Anyone with concerns may also report anonymously by calling the Corporate Compliance Help Line at 1-877-659-5200 or by submitting the form on ethicspoint.com.

Consistent with CW policies, there will be no retaliation against employees, faculty, students, staff, etc. who report concerns in good faith.

24 Sponsored Research (AAHRPP Domain I)

For research that is awarded to MCW directly, refer to applicable policies and procedures of the MCW HRPP and pediatric IRBs.

For research that is awarded to Children's Wisconsin directly, it is CW policy that any sponsored research conducted under the auspices of the CW HRPP is conducted in accordance with federal guidelines and ethical standards.

25 Conflict of Interest in Research (AAHRPP Domain I)

It is CW policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest in the conduct of research.

Conflicts of interest (COI) in research can be broadly described as any interest that competes with an organization's or individual's obligation to protect the rights and welfare of research subjects, the integrity of a research study, or the credibility of the research program. Conflicts of interest can be financial or non-financial.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

25.1 Researcher Conflicts of Interest

Pursuant to the Children's Wisconsin Corporate Compliance Conflict of Interest policy entitled Research Conflict of Interest, CW maintains a Research Conflict of Interest Committee (RCOI Committee). CW HRPP will collaborate with the COI Committee to ensure that COI of investigators and research team members (investigators) are identified and managed before the IRB of record completes its review of any research application.

25.1.1 Procedures

25.1.1.1 Disclosure of Potential COI of Researcher

For CW HRPP purposes, investigator conflict of interest review occurs at the time of new study submission, continuing review, with the addition of a new investigator, and whenever an investigator updates their disclosure(s) indicating a new or changed interest. The disclosure is made by the investigator completing the *CW Conflict of Interest Supplemental Form* found on the CW HRPP website. The Research Compliance office notifies the Institutional official (IO)/Research Conflict of Interest Committee (RCOI Committee) whenever a submission is received which includes the supplemental form that indicates a possible COI. The RCOI committee reviews the investigators' disclosures and either notifies the HRPP staff that no investigator COI was identified or that one or more investigators has an interest that requires evaluation by the RCOI Committee. In the event a conflict that requires disclosure or management is identified, CW Research Compliance office will provide the HRPP a written summary describing the conflict and the conflict management plan (CMP). When the research is under an external IRB, any conflicts identified as the result of COI review and any CMP are provided to the external IRB in accordance with the IRB reliance agreement.

25.1.1.2 Evaluation of COI

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

25.1.1.3 Management of COI

The IRB of record has final authority to determine whether the research, the COI, and the CMP, if any, allow the research to be approved. With regard to the CMP issued by the CW RCOI Committee, the IRB shall either affirm the CMP or request changes to strengthen it. The IRB can require additional measures to manage a COI so that the research may be approved. However, the IRB cannot weaken a CMP approved by the CW RCOI Committee.

For example, in addition to the CMP, the IRB may require:

1. Disclosure of the COI to subjects through the consent process;
2. Modification of the research plan or safety monitoring plan;
3. Monitoring of research by a third party;

4. Disqualification of the conflicted party from participation in all or a portion of the research;
5. Appointment of a non-conflicted PI;
6. Divestiture of significant financial interests; and/or
7. Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB of record may disapprove the research.

25.2 IRB Member Conflict of Interest

Refer to applicable policies and procedures of the MCW pediatric IRBs or the IRB of record.

25.3 Reserved

25.4 Recruitment Incentives

Payment arrangements between or among sponsors, organizations, investigators, research personnel, and those referring research participants present a conflict of interest and may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants (finder's fees) is not permitted. Similarly, payments designed to accelerate recruitment that is tied to the rate or timing of enrollment (bonus payments) are also not permitted. Bonus payments do not include payments for bona fide items or services.

26 Participant Outreach (AAHRPP Domain I)

Children's Wisconsin is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members which will enhance their understanding of human subjects research at Children's Wisconsin and provide them the opportunity to provide input, seek information, and express concerns.

The following procedures describe how Children's Wisconsin fulfils that responsibility.

26.1 Outreach Resources and Educational Materials

1. The HRPP office dedicates a section of the website to research participants entitled "For Participants." This website includes resources, such as Frequently Asked Questions (FAQs), specific to Children's Wisconsin.
2. Designed brochures (Volunteering in Research), and a listing of relevant research-related links.
3. The website includes information regarding how to contact Children's Wisconsin with any questions or concerns about specific research projects or research in general.

4. The website includes a “Contact Us” link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.
5. Children's Wisconsin may periodically provide presentations related to research to community organizations.
6. Children's Wisconsin intends to periodically hold “Research Day” to which members of the public are invited.

26.2 Evaluation

On a periodic basis, Children's Wisconsin evaluates its outreach activities and makes changes when appropriate. In order to formally evaluate its outreach activities, the HRPP RIM will review:

1. The specific community outreach activities being used
2. Whether or not these community outreach activities have an evaluative component (e.g., evaluation instrument distributed to participants), and if so whether feedback is positive, negative, or neutral and if any suggestions were made that could be used to enhance future activities
3. The number of times the participants’ website is visited
4. Feedback provided via the “Contact Us” mechanism on the “Participant Outreach Corner”
5. Feedback provided from other sources (unaffiliated IRB members, investigators, research staff, students, etc.)

The results of the review will be used to establish both the adequacy of current outreach activities and any additional resources that may be needed to meet the needs of the research community regarding participant outreach.

27 Health Insurance Portability and Accountability Act (HIPAA)

See also – CW Corporate Compliance Policies:

- Privacy – Use of Children’s Wisconsin EPIC Care Everywhere for Research
- Privacy – Uses and Disclosure of Protected Health Information (PHI) for Research Purposes

Any questions regarding access, use, or disclosure of Protected Health Information (PHI) of Children’s Wisconsin patients/subjects should be directed to CW Corporate Compliance.

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written or oral) as "protected health information" (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required if the research is subject to the Common Rule, FDA regulations, and/or state laws that provide additional protection for research involving certain categories of health information (such as information derived from HIV/AIDS testing, genetic testing, and mental health records). When research consent is not required by regulation or law (e.g., for exempt research) or the requirement for research consent has been waived by an IRB, the requirements for authorization still apply unless an IRB or Privacy Board has determined that the criteria for a waiver of the authorization requirement are satisfied.

27.1 Definitions

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures. Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting.

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization that includes all of the required elements under the Privacy Rule.

Covered entity. A health plan, a health care clearinghouse, or a health care provider who or that transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and disclosed and how it will be protected.

De-identified. Data is considered de-identified under HIPAA when they do not identify an individual, and there is no reasonable basis to believe that the data can be used to identify an individual. The Privacy Rule defines two methods for de-identifying PHI: (1) when the PHI is stripped of all 18 HIPAA-defined identifying elements and the covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information (Safe Harbor method);

or (2) when an appropriate expert determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information (Expert Determination method).

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, provision of access to, or divulging in any manner, of information outside the entity holding the information.

Genetic Information. Genetic information means, with respect to an individual, information about: (i) The individual's genetic tests; (ii) The genetic tests of family members of the individual; (iii) The manifestation of a disease or disorder in family members of such individual; or (iv) Any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.

Genetic information concerning an individual or family member of an individual includes the genetic information of: (i) A fetus carried by the individual or family member who is a pregnant woman; and (ii) Any embryo legally held by an individual or family member utilizing an assisted reproductive technology. Genetic information excludes information about the sex or age of any individual.

Genetic services. A genetic test; genetic counseling (including obtaining, interpreting, or assessing genetic information); or genetic education.

Genetic test means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal changes. Genetic test does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition.

Health Information. Health Information means any information, including genetic information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual;

the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set. Refers to data sets that exclude 16 categories of direct identifiers that are specified in the Privacy Rule. Limited Data Sets may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, only if the covered entity obtains satisfactory assurances in the form of a Data Use Agreement. Limited Data Sets are not de-identified information under the Privacy Rule.

Minimum Necessary. The least PHI reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for PHI for the research meets the minimum necessary requirements.

Privacy Board. A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research protocol on an individual's privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.

Protected Health Information. Protected Health Information (PHI) means individually identifiable health information that is transmitted by electronic media; maintained in electronic media; or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act (FERPA), as amended, 20 U.S.C. 1232g; in records described at 20 U.S.C. 1232g(a)(4)(B)(iv); in employment records held by a covered entity in its role as employer; and regarding a person who has been deceased for more than 50 years.

Psychotherapy Notes. Psychotherapy notes means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any

summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the covered entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from a researcher or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

27.2 The IRB's Role under the Privacy Rule

Under the Privacy Rule, IRBs have authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although the Common Rule and FDA regulations include protections to help ensure the privacy of subjects and the confidentiality of information (as applicable, to research activities that are regulated under those sets of regulations), the Privacy Rule supplements these protections where HIPAA is applicable, by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

When the IRB of record will not fulfill the functions of a Privacy Board for human subject research, Children's Wisconsin has a privacy board that will make those determinations. This typically occurs when CW is relying on an IRB that is not MCW, and that IRB will not serve as the privacy board (for example, the NCI CIRB). See Corporate Compliance *CW Privacy Board Standard Operating Procedures* for details. The determination will be documented on the CW Corporate Compliance form *CW Privacy Board Determination.* This documentation will be forwarded to the CW HRPP office by Corporate Compliance and the HRPP will store that documentation with the other records for that project. The determination will be communicated to the investigator with the letter published from the CW HRPP that the research can begin at CW.

The Privacy Rule does not change the composition of an IRB. When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the Common Rule and FDA regulations, if applicable, including using either the normal

review procedures (review by the convened IRB) or, as appropriate, the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review.

Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted if the research qualifies for expedited review under Common Rule requirements (See Section 11). 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research protocol, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, because this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of all requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure.

IRB/Privacy Board documentation of approval of a waiver or alteration of the authorization requirement includes:

1. The identity of the approving IRB;
2. The date on which the waiver or alteration was approved;
3. A statement that the IRB has determined that the alteration or waiver or authorization, in whole or in part, satisfies the three criteria in the Rule;
4. A brief description of the PHI for which use or access has been determined to be necessary by the IRB to be necessary;
5. A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and
6. The signature of the IRB Chair or other member, as designated by the Chair, of the IRB, as applicable.

Children's Wisconsin will not release PHI to investigators or other third parties without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

27.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required for research to which the Common Rule, FDA regulations, and/or state laws regarding certain categories of health information apply (although certain research that is subject to the Privacy Rule may be exempt from Common Rule requirements). Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must be written in plain language and contain certain statements and core elements [45 CFR 164.508.6(c)]. At Children's Wisconsin, the HIPAA authorization is documented either within the parental permission/consent documents, or separately from the consent document. All HIPAA authorizations are submitted to the CW HRPP office and the IRB, via the electronic submission platform, to verify that the appropriate template is used without inappropriate substantive modification.

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. See Section 27.12 for more information regarding an individual's right to revoke, procedures, and exceptions.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient such as a Business Associate Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the Common rule or FDA regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner;
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure;
3. The names or other specific identification of the person or persons (or class of persons) to whom the covered entity may make the requested use or disclosure;
4. A description of each purpose of the requested use or disclosure;
5. Authorization expiration date or expiration event that relates to the individual or to the purpose of the use or disclosure (A statement that there is "no expiration date or event" or that authorization expires at the "end of the research study" or "unless and until revoked" by the individual are permissible for research, including authorizations for future research); and

6. The signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices;
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization (if such conditioning is permitted under the Privacy Rule), including research-related treatment and consequences of refusing to sign the Authorization; and
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

27.4 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use of PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or alteration must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later. This is in addition to any other documentation requirements that might apply.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose the PHI contemplated to be used or disclosed for that particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for some defined group of research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some, but not all, required elements or statements of an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    a. An adequate plan to protect health information identifiers from improper use and disclosure;

b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and

c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule;

2. The research could not practicably be conducted without the waiver or alteration; and

3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single IRB or Privacy Board to be used to obtain or release PHI in connection with a multi-site project.

27.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit a researcher to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application or protocol, or identifying potential subjects.

The covered entity must obtain from the investigator representations, either in writing or orally, that (1) the use or disclosure of the PHI is solely to prepare a research protocol or for similar purposes preparatory to research, (2) that the investigator will not remove any PHI from the covered entity (e.g., physically taken out of a facility, or downloaded and retained on the investigator's device) in the course of the review, and (3) the PHI for which access is sought is necessary for the research purpose. [45 CFR 164.512(i)(1)(ii)]

OCR has issued guidance regarding use of a remote access connection for accessing PHI for review preparatory to research. However, CW Corporate Compliance is the final authority on the appropriateness of any preparatory to research activities.

Federal guidance has drawn a distinction between activities that may be undertaken by a researcher who is a member of the covered entity's workforce, e.g., an employee of the covered entity, and a researcher who is not part of the covered entity's workforce. This guidance indicates that researchers may use PHI under the preparatory to research provision to *identify* potential study participants, so long as no PHI is removed from the covered entity and the remaining two representations set forth above can be made. However, the guidance also indicates that researchers may not use PHI obtained pursuant to the "preparatory to research" provision to *contact* potential study subjects unless (i) the researcher is a member of the covered entity's workforce, or (ii) the researcher enters into a BAA with the covered entity. Therefore, if the researcher is not a workforce member or business associate of the covered entity, then the researcher may contact potential subjects only pursuant to a partial waiver of authorization from the cognizant IRB or privacy board, or pursuant to the Authorization of the subject.

At Children's Wisconsin, this is accomplished by the investigator submitting either a Preparatory to Research Attestation to Health Information Management (for projects in development) or a request for a partial waiver of consent and authorization for screening purposes to the IRB of record/Privacy Board via the electronic submissions platform.

27.6 Research Using Decedent's Information

The HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual. When a researcher seeks to use PHI from decedents for a research protocol, the researcher must (1) obtain authorization from the personal representative of the decedent (i.e., the person under applicable law with authority to act on behalf of the decedent or the decedent's estate), (2) obtain a waiver of the requirement to obtain authorization from an IRB or Privacy Board, or (3) attest to the covered entity holding the PHI that the use or disclosure is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, if requested by the covered entity, provide documentation of the death of the individuals about whom information is being sought.

At Children's Wisconsin, the attestation option referenced above is accomplished by the investigator submitting a Research Use of Decedents' PHI Attestation with the submission for proposed research via the electronic submission platform.

27.7 Storage and Use of PHI for Future Research

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. When researchers establish a database or repository containing PHI for the purposes of future research, or intend to maintain PHI following completion of a primary study for potential future research use, individual authorization for the **storage** of PHI for such future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 27.4 for a discussion of waivers of authorization.

An authorization for use and/or disclosure of the stored PHI for **future research** must describe the future research uses and/or disclosures in sufficient detail to allow the potential subject to make an informed decision. The Rule does not require that an authorization describe each specific future study if the particular studies to be conducted are not yet determined. Instead, the authorization must adequately describe future purposes such that it would be reasonable for the subject to expect that their PHI could be used or disclosed for such research. When developing the description of potential future research uses, the investigator should be cognizant of uses of information/specimens that the community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance, including whether any state laws may impose additional consent requirements with respect to any of these sensitive categories of information.

The authorization for future research can be a stand-alone document or may be incorporated into the authorization for the establishment of a database or repository or for the primary

study unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

It is important to note that securing a HIPAA authorization for unspecified future research activities may not, by itself, satisfy all applicable legal consent requirements. The Common Rule, FDA regulations, and state laws also must be considered, as applicable, in evaluating whether the information (including PHI) or identifiable biospecimens may be used for future research projects.

27.8 Corollary and Sub-studies

Consistent with the discussion above relating to future uses of research databases or repositories, the Privacy Rule mandates that subject participation in corollary or sub-studies not essential to the primary aims of the research, such as when PHI form an interventional clinical trial is used to create or to contribute to a central research repository, must be on a voluntary, "opt-in" basis. This is particularly important when the primary research offers a potential direct benefit to the research subject, such as treatment, that might compel the potential subject to agree to an ancillary study, even if the subject would prefer not to do so.

HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

> *"This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization." and "an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals."*

27.9 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule, because information that has been de-identified consistent with the Privacy Rule requirements is not considered individually identifiable health information. The "Safe Harbor" method permits a covered entity to de-identify data by removing all 18 data elements specified in the Privacy Rule that could be used to identify the individual who is the subject of the information or the individual's relatives, employers, or household members. To satisfy the Safe Harbor method of de-identification, the covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers of the individual or his or her relatives, employers, or household members that must be removed are the following:

1. Names;
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people;
    b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Telephone numbers;
5. Facsimile numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers;
13. Device identifiers and serial numbers;
14. Web universal resource locators (URLs);
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including fingerprints and voiceprints;
17. Full-face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that the health information could be used, alone or in combination with other reasonably available information, to identify individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code **is not** derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that are considered de-identified under HIPAA may still be considered human subject data under the Common Rule and may require IRB review and approval. Removal of HIPAA-identifying elements does not necessarily mean that the identity of the subject is not or may not readily be ascertained by the investigator or associated with the information and thus be considered identifiable private information under the Common Rule. The reverse can also be true (and, in practice, is more likely to occur): information may not be "identifiable" under the Common Rule but, because it contains certain HIPAA identifiers, it is considered identifiable under HIPAA.

27.10 Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, PHI in limited data sets may include addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

1. Names;
2. Postal address information, other than town or city, state, and ZIP code;
3. Telephone numbers;
4. Fax numbers;
5. Email addresses;
6. Social Security numbers;
7. Medical Record numbers;
8. Health Plan Beneficiary numbers;
9. Account numbers;
10. Certificate or license numbers;
11. Vehicle identifiers and license plate numbers;
12. Device identifiers and serial numbers;
13. URLs;

14. IP addresses;
15. Biometric identifiers; and
16. Full-face photographs and any comparable images.

Before disclosing a limited data set, a covered entity must enter into a Data Use Agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The DUA establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use or disclosure will be made other than as permitted by the DUA or as otherwise required by law, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use or disclosure, that any agents, including subcontractors, to whom the recipient provides the LDS will agree to the same restrictions and conditions that apply to the recipient, and that the recipient will report any uses or disclosures of the information that they become aware of that are not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through CW Corporate Compliance.

27.11 Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals' access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable Children's Wisconsin authorization template.

27.12 Revoking Authorization

The Privacy Rule establishes the right for an individual to revoke their authorization for uses and disclosures of PHI for research, in writing, at any time, except to the extent that the covered entity has taken action in reliance on the authorization. [45 CFR 164.508(b)(5)] However, individuals providing authorization should be made aware that revoking authorization does not mean that the individual's PHI may no longer be used in the research or be used or disclosed for other purposes.

At Children's Wisconsin, individuals may revoke authorization as described in the Children's Wisconsin Notice of Privacy Practices. When an investigator receives a withdrawal of authorization, s/he should inform Children's Wisconsin HRPP and Children's Wisconsin Corporate Compliance.

A covered entity may continue to use and disclose PHI that was obtained **before** the individual revoked authorization to the extent that the entity has taken action in reliance on the authorization. When the research is being conducted by the covered entity, the covered entity is permitted to continuing using or disclosing the **already obtained** PHI to the extent necessary

to maintain the integrity of the research (e.g., to account for a subject's withdrawal from a study, to report adverse events, or to conduct an investigation of misconduct). A covered entity may also continue to use the PHI for other activities that are permitted under the Rule without authorization (e.g., health care operations such as QA/QI). Additionally, revoking an authorization does not prevent the continued use or disclosure of PHI by a non-covered entity that had **already received** it pursuant to the authorization.

27.13 Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their Protected Health Information made by a covered entity without the individual's authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means use of that information within the covered entity. A disclosure of PHI means "the release, transfer, provision of access to, or divulging in any manner of information outside of the entity holding the information." The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

1. Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.);
2. Disclosures made pursuant to:
    a. Waiver of Authorization;
    b. Research on Decedents' Information; or
    c. Reviews Preparatory to Research.

An accounting is not needed when the PHI disclosure is made:

1. For treatment, payment, or health care operations;
2. Under an Authorization for the disclosure.;
3. To an individual about himself or herself; or
4. As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method. CW Corporate Compliance Policy: Privacy – Accounting for Disclosures of PHI.

28 Special Topics

28.1 Mandatory Reporting

Wisconsin Statute 48.981 addresses reporting requirements for the maltreatment of minors. Under the statute, health care professionals, social workers, hospital administrators and others are mandated to report known or suspected child neglect or physical or sexual abuse. When research is likely to reveal this type of information, investigators must disclose their obligation to report during the consent process. When parental permission and/or child assent are documented using written permission/assent forms, the forms should clearly indicate that the investigator is required to report known or suspected abuse or neglect of a child.

Wisconsin Statute Chapter 252, and Wisconsin Administrative Code DHS 145 address reporting requirements for certain communicable diseases. Under the rule, health care practitioners, health care facilities, medical laboratories, and others are required to report suspected or confirmed cases of certain communicable diseases Wisconsin Department of Health. The Department of Health maintains a current listing of reportable diseases on its website. When research is likely to reveal this type of information, investigators must disclose their obligation to report during the consent process. When consent and/or assent are documented using written consent/assent forms, the forms should clearly indicate that the investigator is required to report communicable diseases that may be identified as a result of eligibility screening or participation in the research.

28.2 Lead Investigator/Coordinating Center

When an IRB of record for a PI or site who is serving as the lead investigator or lead/coordinating center of a multi-site or collaborative research project, the PI must describe within the protocol and IRB application how the research will be overseen and how issues relevant to the protection of human subjects (e.g., IRB initial and continuing approvals, study modifications, reports of unanticipated problems, interim results, data-safety monitoring, etc.) will be coordinated and communicated among participating sites and investigators. For FDA-regulated clinical trials, the plan should address the plan for study monitoring and for the reporting and evaluation of adverse events, significant new risk information, and any other reports mandated by regulation or policy.

The lead PI or lead/coordinating center is responsible for serving as the liaison with other participating sites and investigators and for ensuring that all participating investigators obtain IRB review and approval prior to initiating the research, maintain approval, and obtain IRB approval for modifications to the research. The IRB of record will evaluate whether the plan for research oversight and management of information that is relevant to the protection of human subjects is adequate. See CW Guidance for Multi-Site Activities and Investigator Responsibilities for more information.

28.3 Certificates of Confidentiality

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in 42 U.S.C. 241(d) and in written policies and requirements of certain Federal agencies such as NIH and CDC and are summarized below.

CoC's are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- CoCs are issued automatically when research is conducted or supported by the CDC and involves the collection of identifiable, sensitive information.
- CoCs are issued automatically when research is conducted or supported by BARDA and falls within the scope of the BARDA policy.
- CoCs are issued automatically when research is conducted or supported by HRSA and falls within the scope of the HRSA policy.
- CoCs are issued automatically when research is funded by the FDA in whole or in part and involves the collection or use of identifiable, sensitive information as defined in 42 U.S.C. 241(d).
- Other agencies like SAMHSA and IHS still require a CoC application for research that they fund. NIH maintains a list of CoC Coordinators and Contact Information for Non-NIH HHS Agencies that Issue Certificates.
- Research that is not supported by NIH, CDC, BARDA, HRSA, SAMHSA, IHS, or FDA may still benefit from the protections afforded by CoCs through successful application to the NIH, FDA, or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for research not covered by the NIH policy is available on the NIH CoC Website. Information about discretionary CoC's issued by FDA is available in the FDA guidance document: Certificates of Confidentiality.

28.3.1 Definitions

Identifiable, sensitive information means information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research and

1. Through which an individual is identified; or
2. For which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

28.3.2 Protections and Requirements

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

1. In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, unless the disclosure is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
2. To any other person not connected with the research, unless:
    a. Required by Federal, State, or local laws (e.g., adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described in "1" above;
    b. Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject;
    c. Made with the consent of the individual to whom the information, document, or biospecimens pertains; or
    d. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

Additional Protections

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity. If identifiable, sensitive information covered by a CoC is shared with other researchers or organizations, the researchers or organizations must be informed that the information is covered by a CoC and of their responsibility to protect the information accordingly.

Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent should inform subjects that a CoC is in place and describe the protections and limitations.

28.3.3 NIH, CDC, BARDA, and HRSA

The NIH Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements,*

contracts, other transaction awards, or conducted by the NIH Intramural Research Program, that collects or uses identifiable, sensitive information" that was commenced or ongoing on or after December 13, 2016.

The CDC requirements for CoCs apply to *"CDC supported research commenced or ongoing after December 13, 2016 and in which identifiable, sensitive information is collected, as defined by Section 301(d)."*

The BARDA Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by BARDA, whether supported through contracts, cooperative agreements, grants, other transaction awards, or research ("Awards") that collects or uses Covered Information"* (i.e., identifiable, sensitive information) that was commenced on or after July 17, 2023.

The HRSA Policy on CoCs applies to *"all biomedical, behavioral, clinical, or other research funded wholly or in part by HRSA, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by HRSA staff, that collects or uses identifiable, sensitive information"* that was commenced or ongoing on or after December 13, 2016.

CoCs are automatically granted, and the requirements of such must be complied with, whenever a NIH, CDC, BARDA, or HRSA funded activity falls within the scope of the NIH, BARDA, or HRSA policies or CDC's requirements. Investigators and institutions are responsible for determining when research with NIH, CDC, BARDA, or HRSA support are covered by a CoC.

NIH, CDC, BARDA, and HRSA expand upon 42 U.S.C. 241(d) by explaining that they consider research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects);
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, **regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained;** or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act

Certificates of Confidentiality (CoCs) issued for NIH, CDC, HRSA, or BARDA funded human subject research do not need to be extended or amended while the research remains funded.

If the NIH, CDC, HRSA, or BARDA funding ends, the study will no longer be deemed issued a CoC. While CoC protections remain in perpetuity for already collected or used information, a new CoC will need to be obtained in order to cover any new data collected from already enrolled participants or any new participants. In this case, investigators should request a new CoC following the process for non-federally funded research.

28.3.4 FDA

The FDA requires, as a term and condition of all FDA funding and grant awards, compliance with the requirements of 42 U.S.C. 241(d) when research is funded in whole or in part by the FDA and involves the use or collection of identifiable, sensitive information. Certificates are deemed issued through FDA funding/award terms and conditions and are not issued as a separate document.

Investigators and institutions are responsible for determining when research with FDA support is covered by a CoC and for ensuring compliance with the requirements of 42 U.S.C. 241(d). Awardees are expected to ensure that any investigator or institution not funded by FDA who receives a copy of identifiable, sensitive information protected by these requirements, understand they are also subject to the requirements of 42 U.S.C. 241(d). Awardees are also responsible for ensuring that any subrecipient that receives funds to carry out part of the FDA award involving a copy of identifiable, sensitive information protected by these requirements understand they are also subject to subsection 42 U.S.C. 241(d).

When research is not funded by the FDA but involves "the use or study of a product subject to FDA's jurisdiction and subject to FDA's regulatory authority" (e.g., a clinical investigation of a drug, device, or biologic), the sponsor or sponsor-investigator can request a discretionary CoC from the FDA. Information about discretionary CoC's issued by FDA is available in the FDA guidance document: Certificates of Confidentiality.

Mandatory Certificates of Confidentiality (CoCs) issued for FDA funded human subject research do not need to be extended or amended while the research remains funded. CoC protections remain in perpetuity for already collected or used information; however, a new CoC will need to be obtained in order to protect the privacy of any new human subject research participants from whom identifiable, sensitive information is being collected or used in furtherance of the research, or for new data collected after FDA funding has ended. Researchers could seek a discretionary CoC for such information and data.

28.3.5 Application Procedures for Research Not Automatically Issued a CoC

Any person engaged in human subjects research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH, an

investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

When a researcher is conducting a research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section 299c-3(c)), a CoC is not needed (AHRQ notice NOT-HS-18-012). Investigators should consult with AHRQ when they believe that data might be considered "non-identifiable" or when otherwise uncertain whether a research project falls within the scope of the statute.

When a researcher is conducting a research project that is covered by the Department of Justice (DOJ) confidentiality statute, 28 CFR 22, and/or a NIJ Privacy Certificate, a CoC is not needed because the Privacy Certificate makes identifiable data immune from any legal action.

When research is not funded by the FDA but involves "the use or study of a product subject to FDA's jurisdiction and subject to FDA's regulatory authority" (e.g., a clinical investigation of a drug, device, or biologic), the sponsor or sponsor-investigator can request a discretionary CoC from the FDA. When FDA funds or conducts research, a CoC is automatically issued.

CoCs may also be issued by other Federal agencies and departments, such as SAMHSA or IHS. For research that is supported by SAMHSA or IHS, researchers must contact the respective CoC Coordinator to request a SAMHSA-issued or IHS-issued CoC. Information about the SAMHSA CoC application process, including the extension of protections and amendments to certificates can be found at https://www.samhsa.gov/grants/gpra-measurement-tools/certificate-confidentiality. The IHS CoC contact can be found on the NIH Coc website at CoC Coordinators and Contact Information for Non-NIH HHS Agencies that Issue Certificates.

For more information, see the NIH CoC Website.

28.3.6 IRB Review

Refer to applicable **IRB** policies and procedures of the MCW pediatric IRBs or the IRB of record.

28.4 Databases, Registries, & Repositories

Databases, registries, and biospecimen repositories (all referred to as repositories throughout this section) are used to store data and/or biospecimens for future use.

There are two types of repositories:

- Non-research repositories created and maintained for purposes that are unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.
- Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

28.4.1 Non-research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB approval is required for the research use of identifiable private information or identifiable human specimens from non-research repositories, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of Children's Wisconsin that includes the use of coded private information or specimens, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See Section 4).

Researchers submitting an application for research using data or specimens from non-research repositories must describe the source of the data/specimens and any terms, conditions, or restrictions on use. Data/specimens cannot be used for research if the person from whom the data/specimens originated objected to its use for research. Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

28.4.2 Research Repositories

Research repositories involve three distinct activities:

1. Collection of data/specimens;
2. Storage and management of data/specimens; and
3. Distribution of data/specimens.

Collection

Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Informed Consent information should include:

- A clear description of
    - What data/specimens will be collected;
    - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured;
    - Whether the data/specimens will be identifiable, coded, or deidentified;
    - The types of research to be conducted and any limitations or restrictions on such; and
    - The conditions under which data/specimens will be released to recipient-investigators

- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data and how to make such a request)
- When appropriate, the plan for management of incidental findings and sharing of results

Storage and Management

Repositories should have written policies describing:

- The conditions under which data/specimens will be accepted (e.g., inclusion criteria)
- Informed consent
- IRB review
- The sources of data/specimens
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key; and
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens

Distribution

Repositories should have written policies describing:

- How data/specimens may be requested and by whom
- Any requirements associated with a request for data/specimens (e.g., verification of IRB approval or that approval is not required)
- Any limitations or restrictions on how data/specimens may be used
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will have access to or be provided with the key or other means to re-identify; and
- Agreements with recipient investigators specifying the terms of use.

28.4.3 IRB Oversight

IRB approval is required for the establishment and operation of a research repository when the data/specimens that are accessed, received, stored, or distributed are identifiable. In general, private information or specimens are considered individually identifiable when the identities of the subjects are known to investigators/repository operators or when the data/specimens can be linked to specific individuals either directly or indirectly through coding systems.

Separate IRB approval is required for the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness

of a medical device. Research under the auspices of Children's Wisconsin that includes the use of coded private information or specimens, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See Section 4). The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

28.5 ICH-GCP E6

To facilitate the acceptance of data for regulatory review in participating countries, clinical trials subject to ICH-GCP should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and applicable regulatory requirements. Among other ICH-GCP guidelines, ICH-GCP E6 outlines guidelines for investigators, IRBs, sponsors, and others on how to do so.

When the investigator commits to comply with ICH-GCP E6 as a term of a grant or contract, investigators and the IRB take on additional responsibilities. Investigators are responsible for clearly indicating within their IRB application materials that proposed research is subject to ICH-GCP E6 and for attesting to compliance with ICH-GCP E6 guidelines. The IRB of record will evaluate compliance with the aid of a checklist and by consulting the current ICH-GCP E6 guidance posted by the FDA on it's website.

28.5.1 IRB Responsibilities

In addition to the IRB responsibilities, functions, and procedures outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. An IRB should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects;
2. The IRB/IEC should obtain the following documents:
    a. Trial protocol(s)/amendment(s);
    b. Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial;
    c. Subject recruitment procedures (e.g., advertisements);
    d. Written information to be provided to subjects;
    e. Investigator's Brochure (IB) and available safety information;
    f. Information about payments and compensation available to subjects;
    g. The investigator's current curriculum vitae and/or other documentation evidencing qualifications; and
    h. Any other documents that the IRB/IEC may need to fulfil its responsibilities.
3. The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates that actions were taken;

4. The IRB should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB requests;
5. The IRB should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year;
6. The IRB may request more information than is required by regulation or the ICH-GCP E6 guidance be given to subjects when, in the judgment of the IRB, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects;
7. When a nontherapeutic trial is to be carried out with the consent of the subject's LAR, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials;
8. Where the protocol indicates that prior consent of the trial subject or the subject's LAR is not possible, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations);
9. The IRB should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject; and
10. The IRB should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

28.5.2 Investigator Responsibilities

In addition to the investigator responsibilities outlined elsewhere in this manual, ICH-GCP E6 specifically requires that:

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities;
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor;

3. The investigator should be aware of, and should comply with GCP and applicable regulatory requirements;
4. The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities;
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties;
6. The investigator must have adequate resources to conduct the trial, including:
    a. Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period;
    b. Sufficient time to properly conduct and complete the trial within the agreed trial period;
    c. Adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely; and
    d. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions;
7. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site;
8. If the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated;
9. A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions;
10. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware;
11. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and agrees to the primary physician being informed;
12. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights;

13. Before initiating a trial, the investigator must have written and dated approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects;
14. As part of the investigator's application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure (IB). If the IB is updated during the trial, the investigator should supply a copy of the updated IB to the IRB;
15. During the trial, the investigator should provide to the IRB all documents subject to review;
16. The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol;
17. The investigator may not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects;
18. In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor;
19. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol;
20. The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities for investigational product outlined in section 4.6 of ICH-GCP E6;
21. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding;
22. Additional requirements for Informed Consent -
    a. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use. The subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented;
    b. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's LAR;

c. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's LAR;

d. Neither the investigator, nor the trial staff, may coerce or unduly influence a subject to participate or to continue to participate in a trial;

e. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion;

f. Prior to participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects;

g. If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.

h. Consent for non-therapeutic trials (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) must be obtained from subjects who personally give consent and who sign and date the written informed consent form unless the IRB has expressly approved, in writing, that consent from a LAR is permitted;

i. The consent discussion and written informed consent form should include the following additional elements:

    i. An explanation of the trial treatment(s) and the probability for random assignment to each treatment;

    ii. An explanation of the subject's responsibilities (avoiding any language that appears to restrict subject's rights);

iii. An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access;

iv. An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial;

v. An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant;

vi. When there is no intended clinical benefit to the subject, the subject should be made aware of this;

vii. An explanation that, to the extent permitted by applicable laws or regulations, records identifying the subject will not be made publicly available, and, if the results of the trial are published, the subject's identity will remain confidential; and

viii. A statement that the trial has the approval of the IRB.

23. Investigators must comply with the requirements for records and reports outlined in section 4.9 and 8 of ICH-GCP E6;

24. Investigators must comply with the requirements for safety reporting outlined in Section 4.11 of ICH-GCP E6 including the redaction of personally identifying information; and

25. Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 of ICH-GCP E6 including the requirements for sponsor and IRB reporting.

Approved by:

Peggy Gray

Peggy Troy, President & CEO
Children's Hospital and Health System
March 15, 2024