GUIDANCE
Is My Project Research/Human Subject Research?

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The purpose of this document is to provide guidance on CW HRPP's position regarding what does or does not constitute a research activity. At times it may be difficult to discern whether a proposed activity constitutes research or human subject research. The Children's Wisconsin Human Research Protection Program (CW HRPP) has created tools to help with the assessment.

The responsibility for initial determination of whether an activity constitutes "research" rests with the individual who has 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). Consultation with the HRPP office is encouraged.

The CW HRPP is the sole body designated to make formal written determinations at Children's Wisconsin.

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 CW HRPP office. 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.

Any request for a formal written determination that an activity is research not involving human subjects must include a protocol or other materials in sufficient detail to make the determination.

Notes and important reminders

If you have questions, please request a consultation using our form entitled ***IRB Consultation Request Form***.

To request a formal written determination, please complete the form entitled ***Request for Determination of Human Subject Research.*** The information provided will be reviewed to determine whether the proposed activity would require review and approval by the CW Institutional Review Board (CW IRB), and if not, will serve as written documentation of the determination.

Forms can be found on the CW HRPP website at https://connect.chw.org/departments-services/clinical-departments/childrens-research-institute/human-research-protection/Forms.

DEFINITIONS The following definitions are used to consider what projects constitute research activities within Children's Wisconsin:

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.

Systematic Investigation: 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: 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: 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: 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: 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: 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)].

Identifiable biospecimen: 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)]

Coded: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

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)]

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)]

ACTIVITIES DEEMED NOT TO BE RESEARCH BY THE REVISED COMMON RULE (2018 COMMON RULE REQUIREMENTS)

Under 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.

QUALITY ASSURANCE /QUALITY IMPROVEMENT (QA/QI) ACTIVITIES

QA/QI activities whose purposes are limited to (a) implementing a practice to improve the quality of patient care, and (b) collecting patient or provider data regarding the implementation of the practice for clinical, practical, or administrative purposes do not satisfy the definition of "research" (see above for definition).

Examples of implementing a practice and collecting patient or provider data for non-research clinical or administrative purposes include:

- A radiology clinic uses a database to help monitor and forecast radiation dosimetry. This practice has been demonstrated to reduce over-exposure incidents in patients having multiple procedures. Patient data are collected from medical records and entered into the database. The database is later analyzed to determine if over-exposures have decreased as expected.
- A group of affiliated hospitals implements a procedure known to reduce pharmacy prescription error rates, and collects prescription information from medical charts to assess adherence to the procedure and determine whether medication error rates have decreased as expected.
- A clinic increasingly utilized by geriatric patients implements a widely accepted capacity assessment as part of routine standard of care in order to identify patients requiring special services and staff expertise. The clinic expects to audit patient charts in order to see if the assessments are performed with appropriate patients, and

will implement additional in-service training of clinic staff regarding the use of the capacity assessment in geriatric patients if it finds that the assessments are not being administered routinely.

Quality improvement activities whose purposes are limited to (a) delivering healthcare, and (b) measuring and reporting provider performance data for clinical, practical or administrative uses do not satisfy the definition of research (see above definition). For example, helping the public make more informed choices regarding health care providers by communicating data regarding physician-specific surgical recovery data or infection rates. Other practical or administrative uses of such data might be to enable insurance companies or health maintenance organizations to make higher performing sites preferred providers, or to allow other third parties to create incentives rewarding better performance.

Some Quality Improvement Activities Are Also Research

In certain cases, a quality improvement project may constitute non-exempt human subjects research conducted or supported funded) by HHS or otherwise covered by an applicable FWA. For example, if a project involves introducing an untested clinical intervention for purposes which include not only improving the quality of care but also collecting information about patient outcomes for the purpose of establishing scientific evidence to determine how well the intervention achieves its intended results, that quality improvement project may also constitute nonexempt human subjects research under the HHS regulations.

Doesn't Planning to Publish Make it Research?

Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research; people seek to publish descriptions of non-research activities for a variety of reasons, if they believe others may be interested in learning about those activities. Conversely, a quality improvement project may involve research even if there is no intent to publish the results.

CASE REPORTS REQUIRING IRB REVIEW

CW HRPP does not consider the retrospective review and analysis of medical records for publication of a single case report or a case series involving data from two or three patients to be research, and therefore such a report of 1-3 medical cases does not need to be submitted to the IRB. This is because reporting on such a small number of patients does not involve a systematic investigation, including defining a hypothesis that is then investigated

prospectively and systematically, to develop or contribute to generalizable knowledge. CW HRPP regards such limited case report preparation as an educational activity, not research, and thus it is permissible under the Privacy Rule (HIPAA) as a part of health care operations (45 CFR 164.501) when the case report will be used internally, or in other learning environments, for educational purposes.

When a larger series of patients is being evaluated for presentation or publication, the commonalities of those patients are typically explored and conclusions are drawn (i.e., a systematic investigation). Such a systematic investigation more closely resembles prospectively designed clinical research and as such requires IRB review and approval. While drawing such a "bright line" to distinguish non-research from research may seem arbitrary, it serves as a guide to those who would prepare case reports. If a researcher ever does intend a report of 1-3 medical cases to develop or contribute to generalizable knowledge, or to otherwise constitute research, the report should be submitted to the IRB with a request for a determination whether the case report constitutes research.

Regardless of the number of cases, providers must comply with all applicable laws and CW policies related to the use and release of health information. Permission from the patients who will be included in the report should be sought whenever possible, and journals may require such as a condition of publication. Providers should consult with the CW Research Compliance Manager for guidance on patient privacy and HIPAA.

If needed, the HRPP office can provide a written determination that IRB approval of single case reports or series of up to 3 cases is not required by submitting a ***Request for Determination of Human Subject Research*** form.

RESEARCH THAT IS NOT HUMAN SUBJECT RESEARCH

Under the Common Rule definition of human subject, obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

1. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and
2. using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, private information or specimens are generally individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Conversely, private information or specimens are considered not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, research involving only coded private information or specimens does not generally involve human subjects if the following conditions are both met:

1. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; **and**
2. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:
    a. the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);
    b. there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or
    c. there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

It is the CW HRPP position that the individual(s) providing the private information or specimens and who will serve as the holder of the key (often referred to as "honest broker" or "bank custodian") will have access to the private information and/or specimens outside the context of the research study and are not members of the research team.

In some cases an investigator who obtains coded private information or specimens about living individuals under one of the conditions cited in 2(a)-(c) above may (1) unexpectedly learn the identity of one or more living individuals, or (2) for previously unforseen reasons now believe that it is important to identify the individual(s). If, as a result, the investigator knows, or may

be able to readily ascertain, the identity of the individuals to whom the previously obtained private information or specimens pertain, then the research activity now would involve human subjects under the Common Rule. Unless this human subjects research is determined to be exempt under the Common Rule, IRB review of the research would be required. Informed consent of the subjects also would be required unless the IRB approved a waiver of informed consent.

Comparison to the HIPAA Privacy Rule

The Privacy Rule is a Federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (see 45 CFR part 160 and subparts A and E of part 164). The Privacy Rule permits covered entities under the Rule to determine that health information is de-identified even if the health information has been assigned, and retains, a code or other means of record identification, provided that:

1. the code is not derived from or related to the information about the individual;
2. the code could not be translated to identify the individual; and
3. the covered entity under the Privacy Rule does not use or disclose the code for other purposes or disclose the mechanism for re-identification (see HHS guidance entitled, Institutional Review Boards and the HIPAA Privacy Rule, page 6, Q and A #3, at http://privacyruleandresearch.nih.gov/pdf/IRB_Factsheet.pdf - PDF).

Regarding condition (1) above, in contrast to the Privacy Rule, information that is linked with a code derived from identifying information or related to information about the individual is not considered to be individually identifiable under the Common Rule, if the investigators cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimen pertains. Therefore, some coded information, in which the code has been derived from identifying information linked to or related to the individual, would be individually identifiable under the Privacy Rule, but might not be individually identifiable under the Common Rule.

Questions about the HIPAA Privacy Rule can be directed to the Research Compliance Manager.

RESEARCH INVOLVING CADAVERS

Autopsy material or biospecimens from now deceased individuals is not considered human subject research and does not require IRB oversight. However, there are HIPAA and privacy considerations that will need to be addressed. Please contact the Research Compliance Manager to discuss the project.

Some research in this category, such as genetic studies providing private or medical information about living relatives, may need IRB review. Please contact the CW HRPP to discuss the situation.

Is the activity **designed** (and/or implemented) for **internal CHW purposes in support of the CHW mission?** (See Item 1 of the example on next page)

NO → Submit for IRB approval in IRBNet

YES ↓

Are the activity's findings **designed to be used by and within CHW?** (See Item 2 of the example on next page)

NO → Submit for IRB approval in IRBNet

YES ↓

Is the activity **designed** for the purpose of contributing to **generalizable knowledge** that **expands the knowledge base of a scientific discipline or other scholarly field of study?** (See Item 3 of the example on next page)

YES → Submit for IRB approval in IRBNet

NO ↓

Has the activity been funded as **research?** (See Item 4 of the example on next page)

YES → Submit for IRB approval in IRBNet

NO ↓

Does the activity meet the FDA definition of "**Clinical Investigation**"? (See Item 5 of the example on next page)

YES → Submit for IRB approval in IRBNet

NO ↓

Does the activity involve the use of **double-blind** intervention, **placebo** controls or subjects who would **not normally** receive the intervention under study? (See Item 6 of example on next page)

YES → Submit for IRB approval in IRBNet

NO ↓

Has the purpose of the activity **changed** or been **modified** so that it **fails to meet all of the above criteria for "clinical, practical, or administrative purposes"?** (See Item 8 of the example on next page)

YES → The activity has now become research and it must be submitted for IRB approval in IRBNet before it can continue.

Example:

It has been shown that careful control of blood glucose in diabetic patients recovering from surgery is associated with fewer complications and shorter recovery times. The ICU at an adult hospital ("AH") uses a tracking program to monitor blood glucose levels in diabetic patients recovering from surgery, but has become aware of certain limitations. A newly developed program package in use at other medical centers is gaining wide acceptance.

1. The ICU staff has designed an activity to compare the two monitoring programs using the AH diabetic patients recovering from surgery in the ICU. The activity is consistent with the AH mission that their patients deserve the best care and has been designed/implemented for internal purposes- the AH ICU. At this point it is an operational activity and not research. Operational activities do not need to undergo any sort of review by the IRB nor does the AH HRPP need to be contacted in advance.
2. It is decided to broaden the scope of the activity by including patient data from other ICUs outside the AH and perhaps include children with juvenile onset diabetes. In other words, the activity is no longer designed for internal AH purposes and findings obtained from child subjects are not designed to be used by and within AH. The activity is no longer considered an operational activity. It now must be registered as research.
3. It is decided to include only diabetic patients in the AH ICU with the aim of determining if the new program package provides more reliable information and leads to better patient outcomes at the AH facility. The activity as designed is operational in nature and, as designed, would not be of general interest to the scientific community. Even if other facilities might find the results interesting or applicable, the activity is NOT designed to expand the knowledge base of a scientific discipline or other scholarly field of study. Therefore, it is considered an operational activity and not research.
4. The staff is told that there is research funding for studies of this type. The staff applies for and receives research funds to support the study. Despite the fact that the design is the same, because it is funded as research, it must be submitted for AH IRB review and approval or formal determination.
5. Suppose the new program package includes a blood sampling device that is subject to requirements for prior submission to the FDA. Or suppose the results are to be submitted as part of an FDA application for a research or marketing permit in the future. The activity now becomes a clinical investigation as defined by the FDA and must be submitted for AH IRB review and approval or formal determination.

6. Suppose the activity is designed to include use of placebo controls or double-blind interventions. Suppose patients who normally would not be monitored for blood glucose were also included. Techniques such as these are normally associated with research designs and suggest that this is no longer an operational activity but is designed as a research project. It now must be submitted for AH IRB review and approval or formal determination.

7. The activity is completed and the evidence suggests the new program package is associated with better glucose control, fewer complications and shorter recovery times when used at our medical center. And so, the new program package is adopted for use. A nursing student wants to use the findings to write a paper as part of a degree requirement. The student wants to present the results at a national convention of ICU nurses. The staff wants to publish the results in a journal that focuses on ICU nursing care. Because the activity does not meet the definition of research, no approvals are required to present or publish the findings. If the journal to which the paper is submitted requires peer-review prior to publication, then the investigator(s) may want a formal determination from the AH IRB attesting to the fact that the activity does not meet the definition of research. If this could be anticipated, the request for the formal determination may be made at the outset of the project. If it was not anticipated, the request for formal determination should be made prior to analyzing the data. It should be noted that the nursing student's educational institution may have additional requirements for IRB review and approval. The AH IRB and the nursing student's college or university can be connected to discuss the details of the project.

8. Following up on the data, an investigator notices that the improved tracking software has revealed an apparent correlation between blood glucose levels and a particularly problematic post-operative complication about which little is known. The investigator wants to design a study to systematically reevaluate the data in hopes of demonstrating that the hypothesized correlation is real. The study is now designed to expand the knowledge base of a scientific discipline or scholarly field of study. The study is now research and must be reviewed and approved by the appropriate IRB before it can continue.