Is it a Clinical Investigation?

“Clinical Investigation means any experiment that involves a test article and one or more human subjects.” (21 CFR 50.3 (c))

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

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

Does the project involve a test article?

“any drug (including 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 Services Act at 42 U.S.C. 262 and 263b-363n.” (21 CFR 50.3 (j)) – for more details

Does the project involve human subjects?

“an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.” (21 CFR 50.3 (g))

“Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.” (21 CFR 812.3(p))

Does My Project Require Review by the Children’s Hospital of Wisconsin Institutional Review Board (IRB) (FDA)?

Your project must be submitted to the IRB for regular IRB review.

Written notice of approval must be obtained before research activities begin.

Special Circumstances:
Not research but IRB Submission is required

HUD - Humanitarian Use Device

Expanded Access Use
(emergency and non-emergency)

Check the HRPP Web pages for more information

Activities that constitute “human subject research” are regulated by U.S. federal law by both the U.S. Food and Drug Administration (FDA) and the U.S. Department of Health and Human Services (DHHS).

The FDA regulations apply to projects that involve an FDA regulated product – thus are narrower than the HHS regulations regarding what constitutes human subjects research.

Your project may not meet the FDA definition, but still involve human subjects research (per the HHS regulations) and require IRB review.

If you determine that the FDA regulations do not apply, you still need to analyze the project based on the HHS definitions of human subject research, which are broader and apply to more types of research. See the next flowchart.
Does My Project Require Review by the Children’s Hospital of Wisconsin Institutional Review Board (IRB) (HHS)?

Is it research?

* a “systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge?”

(45 CFR 46.102(d))

Does it involve Human Subjects?

* 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.

(45 CFR 46.102(f))

Your project must be submitted to the IRB for either a determination of exemption OR regular IRB review.

Written notice of approval must be obtained before research activities begin.

Activity does not meet the definition of research. IRB review and approval is not needed.

Activity does not meet the definition of human subject research. IRB review and approval is not needed.

If you are still uncertain whether your project is human subject research needing IRB review and approval, or you need a formal determination letter from the IRB, submit a **new project** package to request a determination. Submit a cover letter requesting the determination and a detailed summary of the project.

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Created January 6, 2017- Children’s Hospital of Wisconsin IRB
Does My Project Using Secondary or Existing Data Require Review by the Children's Hospital of Wisconsin Institutional Review Board (IRB)?

- Are the data/specimens about or from individuals who are or may still be living? 
  - Yes, Activity does not meet the definition of research. IRB review and approval is not needed.
  - No, Are the specimens from a producer or supplier of public use data; OR Is ALL of the information about specimens/data available in the public domain?
    - Yes, Can the data recipient link the specimens/data directly to identifiable living individuals? 
      - Yes, Is the data provider a collaborator in the data recipient's research? (i.e. involved in the design, conduct, or reporting, listed as a collaborator, planned sharing of authorship credit?)
      - No, Are the data/specimens provided with a code linking them to identifiable living individuals? 
        - Yes, Can the recipient readily identify individuals to whom the data/specimens are linked? Examples of when recipient cannot link data/specimens to living individuals
        - No, Involves interaction or intervention
    - No, Were/will specimens/data (be) collected specifically for the proposed project through interaction or intervention with living individuals?
      - Yes, Your project must be submitted to the IRB for either a determination of exemption OR regular IRB review. Written notice of approval must be obtained before research activities begin.
      - No, Doesn't involve interaction or intervention

“Research Involving Private Information or Biological Specimens Flowchart”, National Institute of Health (NIH), January 2006"
What is a systematic investigation?

**Systematic Investigation** is typically a predetermined method for studying a specific topic, answering a specific question(s), testing a specific hypothesis(es), or developing theory.

- Includes observational studies, interview or survey studies, group comparison studies, test development, and interventional research.
- Data or information is collected in an organized and consistent way.
- Includes ideas about what the investigator wants to learn and how best to learn it.
- Involves a prospective plan.
- Data or information is analyzed in some way.
- Conclusions can be drawn from the results.

Projects that are not systematic investigations include oral histories, journalism, phenomenological activities.

Program evaluation may or may not meet this definition based on design and intent. Projects may be systematic investigation but they still may not fit the definition of research.

What is generalizable Information?

Generalizability is not specifically described or defined in the regulations. **Intent is important.** Developing or contributing to generalizable knowledge means that the intent or purpose of the systematic investigation is dissemination of findings.

- Information collected is intended to be applied beyond a particular patient/setting/program.
- Intent of the research is to add information to the field of study. Results applied beyond the subject population to other settings.
- Intent to test or develop scientific hypotheses, draw conclusions to be shared beyond the populations or situations being studied.
- The knowledge contributes to a theoretical framework of an established body of knowledge.
- **The primary beneficiaries:** other researchers, scholars and practitioners in the field of study.
- The results are expected to be generalized to a larger population beyond the site of data collection.
- The results are intended to be replicated in other settings.
- Involve critical evaluation of data.

Common ways of disseminating results include publishing or presenting. HOWEVER, intent to publish is not the sole criteria. If the published materials will be limited to only documenting or reporting on events, situations, policies, institutions or systems without the intent to form hypotheses, draw conclusions, or generalize findings, this does not make the project research. Most now agree publication does not make a project ‘research’ per se (OHRP even recognizes this fact in its [Quality Improvement Activities FAQs](https://www.ohrs.hhs.gov/qualityimprovementactivities)).
“If I plan to carry out a quality improvement project and publish the results, does the intent to publish make my quality improvement project fit the regulatory definition of research?

No, the intent to publish is an insufficient criterion for determining whether a quality improvement activity involves research. The regulatory definition under 45 CFR 46.102(d) is “Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.” 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 nonresearch 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.”

If you plan to publish the results of a QI activity and you anticipate a publication needs a formal determination letter from the IRB stating the project was not Human Subject Research, you can submit the project through IRBNet as a new project and indicate under type of protocol that this project is QI/QA and in a cover memo indicate you would like a formal determination. An IRB chair will review and you will receive written notification of whether the IRB agrees that the project is not human subject research.

Quality Improvement (QI) is not considered research if the main intent of the QI is to inform or improve a local process. If outcomes will remain specific to the organization, programs or services the project is not research. However, if your primary intent is to generalize the results outside of your local area for other organizations, programs, or services the activity is research. Typically, quality assurance or improvement activities do not require IRB review when activities involve the implementation of an accepted practice to improve the delivery or quality of care or services (including, but not limited to, education, training, and changing procedures related to care or services) if the purposes are limited to altering the utilization of an accepted practice and collecting data to evaluate the effects on the utilization of the practice. In these cases, the QI activities are designed only to improve the implementation of a practice that is already accepted, not to evaluate the effectiveness and value of the practice itself. Some QI projects may contain aspects that would be considered research and would therefore need IRB review.

**Quality Improvement Activities:** [Quality Improvement Activities FAQs](#)

Quality improvement is defined as “systematic, data-guided activities designed to bring about immediate improvement in health care delivery in particular settings” * Traditional QI/QA projects are designed, or intended, to principally:

- Improve patient care:
  - Compare a program/process/system to an established set of standards such as standard of care, recommended practice guidelines or other benchmarks
  - Improve the performance of institutional practice or local systems
  - Bring about improvements in health care delivery
  - QI projects generally are integrated with routine patient care
- Improve a process, program or system
- Be adaptive in nature, the protocol will change based on what is learned
- Consider established or accepted standards of performance for comparison

Some features of QI activities are shared with research:

- Application of a methodology
- Systematic collection of data

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• May include patient data
• Publications of findings
• Involve human participants
• Are concerned with inquiry
• Testing solutions
• Are processes in which empirical or systematic inquiry generates a question that data collection is designed to answer

Activities that start out as QI projects may eventually lead to research when a decision is made to use previously collected QI data for research purposes
• If a project progresses to this level, IRB review is required

Many student projects do not contribute to generalizable knowledge because the intent or purpose of the project is to complete the requirements of the course. However, if the student project may lead to the use of the results outside of the specific course, e.g. for a publication, thesis or dissertation this may be research and require IRB review.

Why does “about whom” matter?
Consider if the project focuses on the person or if the focus is on policies, practices or procedures about which the person is knowledgeable.

A project is “about” individuals when the focus of the project is on people or their opinions, perceptions, choices, decisions regarding themselves or how methods, policies, procedures, organizations, etc., affect them or their environment.

Projects which collect information about policies, practices or procedures – even if the person who provided that information is identified – do not constitute human subject research. (When the focus of the project is only on products, methods, policies, procedures, organizations: e.g., interviewing transportation staff and officials about parking or transportation policies and procedures.)

What is an interaction?
An interaction may be communication or interpersonal contact between the investigator (or research team) and the living individual. Examples include interviews, questionnaires, surveys, observations, manipulations of subject behavior, diet, or environment, physical measurements, specimen collection (e.g. blood tissue), and administration of experimental drugs or devices.
• Does not have to be face to face
• Can be entirely on paper or electronic
• EG: online surveys that don’t ask for identifying information is still an “interaction”
• Participant observation is a variant of interaction

What is an intervention?
An intervention may be physical procedures (e.g. venipuncture) or manipulations of living individuals or the living individuals’ environments.
What is private identifiable information?

Identifiable means if 1) the identity of the individual from whom the information was obtained is ascertained or may be readily ascertained by the investigator; or 2) the identity of the individual from whom the information was obtained is associated or may be readily associated with the information.

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

Examples of identifiable, private information include the subject’s name, address, phone number, social security number, medical record number, student or employee identification number, or in some cases, the combination of data such that they can identify a single individual through deductive reasoning. For example, data about employer, job title, age and gender may not individually identify a subject, but when combined, could in certain cases, identify a specific individual.

What is NOT considered identifiable, private information: If the information cannot be linked to a living individual, or is considered public or is given with the expectation that it will be made public and that it will be linked to the individual (e.g. biography or news story), then it would not be considered private identifiable information. For example, use of a publicly available data set that does not contain identifiers or codes linked to individuals does not involve human subjects research. However, use of a publicly available data set that does contain identifiers or codes linked to individuals does involve human subject research.

If you obtain specimens or data that have already been collected by someone else for some other purpose, and are not linked to any identifiers that would make it reasonably possible to identify an individual, the activity is not considered research with human subjects.

What is a determination of exemption?

Sometimes a project may meet the definitions of “research” and “human subject” but may also fall under one of the 6 exempt categories - if the only involvement of human subjects will be in one or more of the stipulated categories projects are exempt from this policy in which case they do not fall under the scope of the HHS regulations and IRB oversight may not be required (45 CFR 46.101 (b) (1-6))

- “Exempt” means exempt from the regulations, not necessarily from IRB review
- Only applies to research that is no more than minimal risk (45 CFR 46.102(i))
- None of these categories apply to research with prisoners, pregnant women, or other vulnerable populations
- Regulations do not specify who is to make the determination on whether a project falls into one of these categories. At CHW it is the IRB – submission is required for the IRB to review and verify exempt status.

If you determine a project is in fact human subject research, and think it may fall under one of the exempt categories, this requires a submission to the IRB to verify exempt status

- submit the project as a new research project through IRBNet and include the form/checklist for exempt categories
- This will be forwarded to one of the IRB committees who will issue a letter of determination (NOT approval) regarding whether they are in agreement that the project is exempt
- Determination that project is exempt - the IRB will not conduct subsequent reviews of the study.
  - Amendments (changes) to exempt studies should be submitted to the IRB for review because the change may make the project no longer exempt
You will still need to get consent
Subject should still be told this is research
You still need to protect the subjects’ privacy

- **Determination that project is NOT exempt** – it will proceed with normal IRB review as a new project (either full board or expedited)

**OHRP Decision Charts regarding exemptions**
**Exempt Research Determination FAQs**
**Categories of Exempt Research (45 CFR 46.101(b) (1-6))**
**OHRP Guidance – Exempt Research and Research That May Undergo Expedited Review**

**NOTE ON HIPAA:** HIPAA Privacy rule – 45 CFR 160 and 164) still applies to all exempt research that uses protected health information. They do not apply if the PHI has been de-identified.

**Examples of when recipient cannot link data/specimens to living individuals**

- Key to decipher code is destroyed before research begins
- Investigators and holder of the key to the code enter an agreement preventing release of key to investigators under any circumstances
- There are IRB approved written policies in place preventing the release of the key under any circumstances
- There are other legal requirements prohibiting the release of the key under any circumstances

**Regular IRB review**

Human subject research that is not exempt requires review and approval and continued oversight by the IRB. If the study requires **full board review** it will be added to an agenda for the regularly scheduled IRB meetings. Anything that does not qualify for expedited review must go to the full board. The CHW IRB meets twice a month on the first and third Wednesday. At these meetings studies are reviewed and voted on by the full committee.

Your study might meet criteria to be **expedited**.

- Expedited review procedures are allowed for certain kinds of research involving **no more than minimal risk** (45 CFR 46.102(i)), and for minor changes in approved research.
- Expedited does not mean “quick” or “immediate.” Regulations require that an expedited review be given the same scrutiny that a submission to the full board would receive. Pre-review, modifications requests, compliance review all still take place and can take some time before approval is granted. However, rather than being reviewed by the full committee, the review is conducted by the IRB Chair, or by one or more experienced reviewers designated by the Chair from among IRB members. This review takes place outside of the regularly scheduled IRB meetings.
- An expedited reviewer can Approve or require modifications but cannot **disapprove** a study. In that case, your study would require Full Board review.
- The IRB may, in some circumstances, require full board review even if a study meets the regulatory requirements for expedited review.
- Expedited review categories 8 and 9 only apply to continuing review.

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Health and Human Services Office of Research Protection expedited review categories

FDA Expedited Review 21 CFR 56.110
OHRP(HHS) Expedited Review 45 CFR 46.110
OHRP Decision Charts regarding expedited review

Other tools:

Decision Trees from HHS.GOV

The Office for Human Research Protections (OHRP) provides the graphic aids as a guide for institutional review boards (IRBs), investigators, and others who decide if an activity is research involving human subjects that must be reviewed by an IRB under the requirements of the U.S. Department of Health and Human Services (HHS) regulations at 45 CFR part 46.

National Institutes of Health (NIH) Infopath Questionnaire

This is a series of branching logic questions that may help determine if your project involves human subjects, may be exempt from regulations, or is not considered human subjects research. This should not be used as the sole determination of whether an exemption applies, if you think a project is exempt this should still be submitted to the CHW IRB for a formal determination.

CITI Program

Learner group 3 includes a module “Defining Research with Human Subjects” that may be helpful. You will need to log into your account, and add Learner Group 3 under “Add a Course” if this does not already show up under your courses. Within this group is the module.