Marshfield Clinic

Human Participants in Research & the Human Research Protection Program

1. SCOPE

1.1. System-Wide

2. DEFINITIONS & EXPLANATIONS OF TERMS

2.1. **Anonymous**:

- No identifiers or codes on project materials that could link the data with individual participants. Even the research investigator cannot discern the identity of participants.

2.2. **Emergency Research**:

- Research defined as emergency research at 21 CFR 50.54, for which informed consent may be waived under specific circumstances, is not currently conducted at Marshfield Clinic.

2.3. **Engage in Research**:

- To intervene or interact with human participants, or obtain private individually identifiable information about human participants, for purposes of research.

2.4. **Feasibility Study**:

- Analysis and evaluation of a proposed project that is initially carried out to assess the desirability or practicality of further development. Such studies are typically performed during the planning stages.

2.5. **Generalizable Knowledge**:

- 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 the specific study population), to inform policy, or to provide general, applicable conclusions.

2.6. **Human Participant or Human Subject**:

- Under the Common Rule [45 CFR 46.102(f)], "human subject" (also referred to as human participant) is a living individual about whom an investigator conducting research obtains: 1) data through intervention or interaction with the individual or 2) identifiable, private information.
  - ◊ "**Intervention**" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulation of the participant or the participant's environment that are performed for research purposes.
  - ◊ "**Interaction**" includes communication or interpersonal contact between investigator and participant.
  - ◊ "**Private information**" is information that is not available to the general public, and includes information about behavior that occurs in the 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. Private information must be *individually identifiable* in order for obtaining the information to constitute research involving human participants.

- Under FDA regulation [21 CFR 56.102(e)], "human subject" (also referred to as human participant) is an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A participant may be either a healthy human or a patient. If the research involves a medical device, individuals are considered "subjects" or "participants" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control [21 CFR 812.3(p)].

2.7. **Individually Identifiable**:

- The identity of living individuals is, or may readily be, ascertained by the investigator or associated with the information.
  - ◊ At a minimum, data containing an individual's name, street address, social security number or phone number would be considered individually identifiable.
  - ◊ Also includes circumstances where private information or specimens can be linked to specific individuals by the investigator, either directly or indirectly through coding systems (e.g., medical history number or other code linked to a legend including a direct identifier, such as name). However, OHRP does not ordinarily consider information to be individually identifiable if: (1) the investigator and the holder of individually identifying information sign an agreement prohibiting the release of individually identifying information to the investigator under any circumstances, or (2) there are other legal requirements prohibiting the release of the link to the investigator.

2.8. **Research**:

- Under the Common Rule [45 CFR 46], "research" is a systematic investigation including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute "research" for purposes of this policy, 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.
- Under FDA regulations [21 CFR 56.102(c)], the terms research, clinical research, clinical study, study, and clinical investigation are synonymous. Under FDA regulations, activities are "research" when they involve:
  - ◊ Use of a drug other than the use of an approved drug (approved by FDA for marketing) in the course of medical practice [21 CFR 312.3(b)]; or
  - ◊ Use of a medical device other than the use of an approved medical device (approved by FDA for marketing) in the course of medical practice [Food, Drug and Cosmetic Act 530(g)(3)(a)(i)]; or

◊ Gathering data that will be submitted to or held for inspection by FDA in support of an FDA marketing permit for a food, including a dietary supplement that bears a nutrient content claim or a health claim, an infant formula, a food or color additive, a drug for human use, a medical device for human use, a biological product for human use, or an electronic product [21 CFR 50.1(a) or 56.101(a)].

2.9. **Systematic Investigation**:

- An activity that involves a prospective plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a question.
- Activities are not research if they do not involve a systematic approach involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory.

3. POLICY BODY

3.1. Guiding Principles and Law

a. Marshfield Clinic and Marshfield Clinic Research Foundation Institutional Review Board (MCRF IRB) are guided by the ethical principles set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, otherwise known as the Belmont Report.

- "Beneficence" is the consideration of whether the sum of the benefits to the research participant or society, and the importance of the knowledge to be gained from the research, outweigh the risks to the participants, warranting the research.
- "Respect for Persons" requires legally effective informed consent to be obtained, unless the requirements for waiver of informed consent are met. Autonomy is also respected.
- "Justice" requires the selection of participants to be equitable and representative of the group that will most likely benefit from the research.

b. Clinical trials subject to ICH-GCP (E6) will be conducted in accordance with ethical principles within the Declaration of Helsinki and will be consistent with good clinical practice and the applicable regulatory requirements.

c. Marshfield Clinic will comply with the Department of Health and Human Service (DHHS) regulations for the protection of human subjects (45 CFR 46) for all research, the Food and Drug Administration regulations for the protection of human subjects (21 CFR Parts 50 and 56) when applicable, and Marshfield Clinic's approved Federal Wide Assurance (FWA0000873), on file with the Office for Human Research Protection (OHRP). The HIPAA Privacy Rule, and Wisconsin state and local laws will also be followed.

d. State and local laws supersede federal laws and regulations whenever state and local laws provide additional protections over and above those provided by federal law. Conflicts between federal and state laws are resolved in favor of the laws that are most protective of the research participant. Marshfield Clinic Legal Services will be consulted as needed.

e. When research is conducted outside the state of Wisconsin, Marshfield Clinic Legal Services will be consulted.

3.2. Components Involved in Human Research Protection and Their Responsibilities, Authorities and Interactions

a. Executive Director of Marshfield Clinic Research Foundation (MCRF)/Institutional Official

The Executive Director of MCRF is the Institutional Official ultimately responsible for the Human Research Protection Program (HRPP). The Executive Director of MCRF will allocate resources necessary to ensure adequate protection of human research participants, and will ensure the development and maintenance of a research program that fosters the integrity of research and the protection of research participants. The Executive Director of MCRF will ensure that no one who is responsible for business development of the organization will be responsible for the day-to-day operations of the IRB. As part of the HRPP, the Executive Director of MCRF will work with the Office of Research Integrity & Protections (ORIP) to establish and maintain an Institutional Review Board (IRB), hereinafter referred to as the Marshfield Clinic Research Foundation IRB (MCRF IRB). The Executive Director of MCRF appoints the Chairperson of the IRB and approves all IRB members, and assures the IRB functions independently and free from coercion and undue influence.

b. Institutional Review Board (IRB)

MCRF IRB will have all authorities granted to it under 21 CFR 56 & 45 CFR 46 and Marshfield Clinic's FWA, including but not limited to the following:

- To approve, require modifications to secure approval, or disapprove all research activities overseen and conducted by the Organization
- To suspend or terminate IRB approval of research not being conducted in accordance with the IRB's requirements or that have been associated with unexpected serious harm to participants
- To observe, or have a third party observe, the consent process and the conduct of the research.

No institutional official or committee may approve a human participant research activity that has not been approved by the MCRF IRB.

Other IRBs designated by Marshfield Clinic also have the authority to review and approve human participant research on its behalf.

MCRF IRB has the authority to review human participant research for other institutions under IRB Authorization Agreements (IAAs)

c. Office of Research Integrity & Protections (ORIP)

ORIP, under the guidance of the Executive Director of MCRF, has primary responsibility for the oversight and development of the Human Research Protection Program (HRPP). The IRB Chair is housed within ORIP, as is the IRB Administrator and IRB support staff. ORIP coordinates all IRB operations, develops HRPP policy, maintains IRB documentation, coordinates and provides education, answers queries of investigators, IRB members and staff,

communicates pertinent information about human research rule changes to all components of the HRPP, and continually strives to improve operational efficiencies and enhance the quality of the program.

d. IRB Chairperson, IRB Members, IRB Staff, Marshfield Clinic Investigators, Employees & Students

- IRB Chairperson, IRB members, IRB staff, and all employees or students engaged in or helping to support the conduct of human participant research have an ethical obligation to protect the rights and welfare of the research participants. These individuals will follow all applicable regulations, as well as institutional and IRB policies. Investigators will ensure research involving human participants receives prior and ongoing IRB approval and will follow any project-specific directives issued by the IRB.

e. Research Conflict of Interest Committee (RCOIC)

- The RCOIC is also appointed by Executive Director of MCRF and administered by Office of Research Compliance. The RCOIC reviews all financial and associational interests of investigators, and communicates any identified conflicts and related management plans to the IRB prior to IRB review.

f. Research Committee

- The Research Committee reviews the scientific validity of research activities that involve greater than minimal risk and have not been reviewed by an impartial external review body. The IRB receives Research Committee minutes and correspondence detailing the outcome of such review. The Research Committee is appointed by the Executive Director of MCRF.

g. Research Compliance Officer

- The Research Compliance Officer (RCO) will have oversight of compliance with the requirements of this policy. Upon request, the RCO will be provided with documentation from any of the components involved in human subject protection that substantiates that all provisions are current and being followed in day-to-day operations. If suspected non-compliance in human subjects research is identified, the RCO will direct the researchers to follow the steps to report the non-compliance in accordance with the Non-Compliance with Federal Regulations, Institutional Policies, and IRB Approved Applications & Protocols policy.

h. Corporate Compliance Officer

- The Corporate Compliance Officer (CCO) is responsible for compliance across the Marshfield Clinic system. The RCO reports to and receives direction from the CCO. The RCO keeps the CCO apprised of human subject protection related compliance issues. The CCO provides guidance on corrective and preventative action, as necessary.

i. Research Compliance Educator (RCE)

- Under the direction of the RCO, the RCE monitors compliance with the requirements of this policy, and develops and presents education and

training as necessary. Research Quality Improvement and best practices are also a focus of the RCE.

j. Legal Services

- An attorney from Marshfield Clinic's Legal Services Department attends IRB meetings and provides legal counsel at the request of the IRB.

3.3. When IRB Review and Approval Is Required

a. IRB review and approval, by either the MCRF IRB or other IRB as designated by Marshfield Clinic, is required prior to initiation when:

- The activity meets the definition of human subject or human participant and research; AND
- Marshfield Clinic physicians or staff are engaged in the research, as defined above, regardless of sponsorship.
- Examples include:
  - Clinical trials;
  - Prospective or retrospective data collection;
  - Databases, specimen repositories, and subsequent projects using them. See the document, "IRB Review of Databases, Registries and Bio-banks;" and
  - Humanitarian Use Devices, although an exception to the research rule. See MCRF procedure, "Humanitarian Use Devices."
  - Laboratory-based human subjects research

b. When there is uncertainty as to whether a proposed activity is human subject or human participant research, the investigator should complete the "IRB Review Determination Request" form. The IRB Chair, IRB Administrator, or a Compliance Analyst within ORIP will use the information provided to compare the activity against the definitions of "human subject" or "human participant" and "research" in order to make a determination. Determinations will be made and communicated in writing promptly (normally within 5 working days). If it is determined that the activity is human subject or human participant research, the investigator will be instructed to submit an IRB application for IRB review. If it is unclear whether the proposed activity qualifies as human subject or human participant research, the individual attempting to make the determination may ask the investigator to complete an IRB application or otherwise provide additional written information in order to allow for a final determination.

3.4. When IRB Review and Approval is Not Required

a. IRB review is not required by MCRF IRB or another IRB designated by Marshfield Clinic when activities do not meet the definition of human subjects or human participants research *or* if Marshfield Clinic physicians, staff, or facilities are not engaged in the human subjects or human participants research.

Examples include:

- Research involving only data that is not individually identifiable, or anonymous samples;
- Certain quality improvement projects. See the document, "Program Evaluation including Quality Assurance and Quality Improvement, Determining the Need for IRB Review;"
- Most case reports. See the MCRF document, "Case Reports;"
- Research in which Marshfield Clinic physicians or staff are subjects participating in research conducted by an external organization;
- Feasibility studies are, in most instances, considered preparatory to research, and therefore do not require IRB review. However, if any feasibility data is to be kept by the researcher, the feasibility study must have prior IRB approval;
- Emergency use of an investigational drug or biologic. See the document, "Expanded Access to Investigational Drugs or Biologics or Devices;"
- Exempt research, as determined by ORIP. See the document, "Exempt Projects, Review of."
- Secondary use of coded research data or specimens if:

  The private information or specimens were not collected specifically for the currently proposed research project ; and

  Investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

  The investigators and holders of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances; or

  There are IRB-approved written procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances.

- Non- Marshfield Clinic investigators planning to use Marshfield Clinic facilities for their research. In this case, ORIP review of the research plan is required to determine whether the Clinic is "engaged."

3.5. Initiating IRB Review of Human Subjects/Participants Research

a. Investigators planning to conduct human subjects research must submit an application along with supporting documentation to ORIP so that IRB review may be scheduled, and IRB approval obtained, prior to the initiation of research.

3.6. Institutional Approvals

a. Even if a research project has been approved by MCRF's IRB, the Executive Director of MCRF may disapprove or impose any condition to the conduct of such research.

b. Principal Investigator will be notified in the IRB approval letter that there may be institutional approvals necessary beyond the IRB approval. Other institutional approvals may include, but are not limited to:

- Research Committee and Board of Trustee or Executive Director approval of internally funded research
- Clinical Research Center approval of industry-sponsored clinical trials
- Sponsored Programs approval of federal grant and contracts and private agency awards
- Department or Center approval

c. The Executive Director of MCRF will be informed of projects approved by the IRB by receiving a copy of IRB convened board and expedited review minutes.

d. The Executive Director of MCRF is responsible for notifying the Principal Investigator of any study he/she chooses to disapprove or place conditions upon. The notification should be provided in writing and a copy provided to the IRB.

3.7. Detailed Policies and Procedures

a. The Office of Research Integrity & Protections will maintain policies and procedures adequate to convey specific requirements and inform IRB members, IRB staff, and all employees or students engaged in or helping to support the conduct of human participant research of the processes for seeking initial and ongoing approval of human participant research. These documents will be maintained electronically and made centrally available within its electronic software system. Changes to these documents will be summarized in institutional newsletters.

3.8. Attempts to unduly influence IRB members and IRB staff

a. Any attempt to unduly influence IRB members and/or IRB staff in the performance of their IRB duties should be reported to the IRB Chair who consults with the Executive Director of MCRF when needed. If the attempt to unduly influence IRB members is made by the IRB Chair, members should consult with the IRB Administrator, the Research Compliance Officer or the Executive Director of MCRF. If the undue influence attempt is made by the Executive Director of MCRF, the IRB Chair should consult with the Chair of Marshfield Clinic's Board of Directors.

b. Any attempts to unduly influence the IRB Chair in the performance of his or her IRB duties should be reported to the Executive Director of MCRF or, in the alternative, to the Chair of Marshfield Clinic's Board of Directors if the undue influence attempt is made by the Executive Director of MCRF.

c. Attempts to unduly influence the IRB Chair, members, or staff will be handled by the IRB Chair and/or Executive Director of MCRF and/or Chair of Marshfield Clinic's Board of Directors as follows:

- A prompt and thorough investigation of all allegations of attempts to unduly influence the IRB Chair, members and/or staff will be conducted.

- A written report will be submitted to the Executive Director of MCRF, or, in the alternative, to the Chair of Marshfield Clinic's Board of Directors, describing the incident, the investigation and actions taken.
- Appropriate corrective action will be taken to ensure that decisions of IRB members and/or staff are not or have not been unduly influenced.
- Using appropriate methods, the IRB Chair or Executive Director of MCRF or Chair of Marshfield Clinic's Board of Directors will communicate to the IRB Chair, members, staff and researchers the inappropriateness of attempts to unduly influence IRB members and/or staff in the performance of their IRB duties. Additional disciplinary action may be taken as deemed appropriate.

3.9. Questions, Concerns and Suggestions

a. Researchers and research staff may contact the IRB Chair, IRB Administrator, or Research Compliance Officer via email or phone to obtain answers to questions, express concern, or convey suggestions about the Human Research Protection Program. Concerns and suggestions will be considered collectively by these individuals. Depending on the complexity of the question asked, these individuals may request additional written material prior to issuing a response.

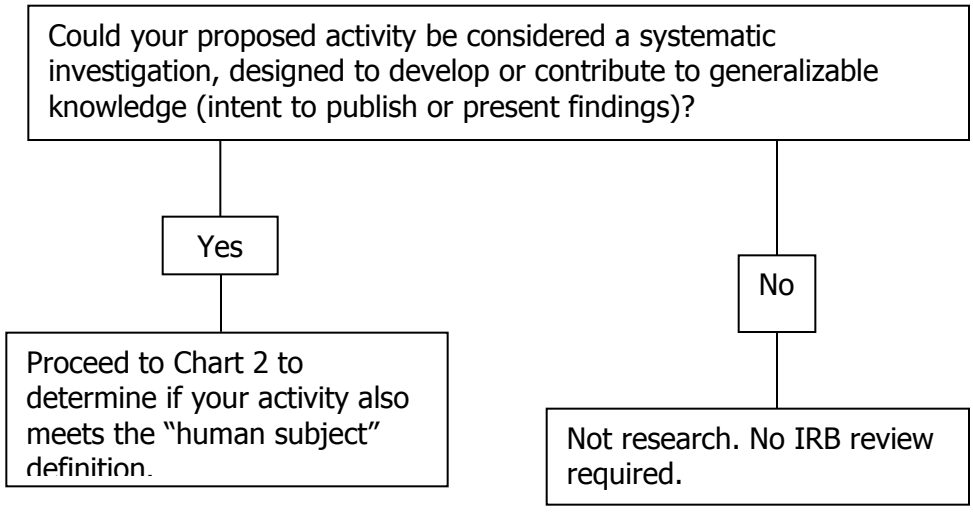
4. DECISION CHARTS

Human Research Subject Review Decision Chart

The Institutional Review Board (IRB) oversees the protection of human subjects involved in research. The purpose of charts 1 & 2 is to determine if your proposed activity meets the definition of both "research" and "human subject" and, therefore, requires review by the IRB.

Chart 1: Definition of Research

- The purpose of this chart is to determine if the definition of "research" is met in your proposed activity.

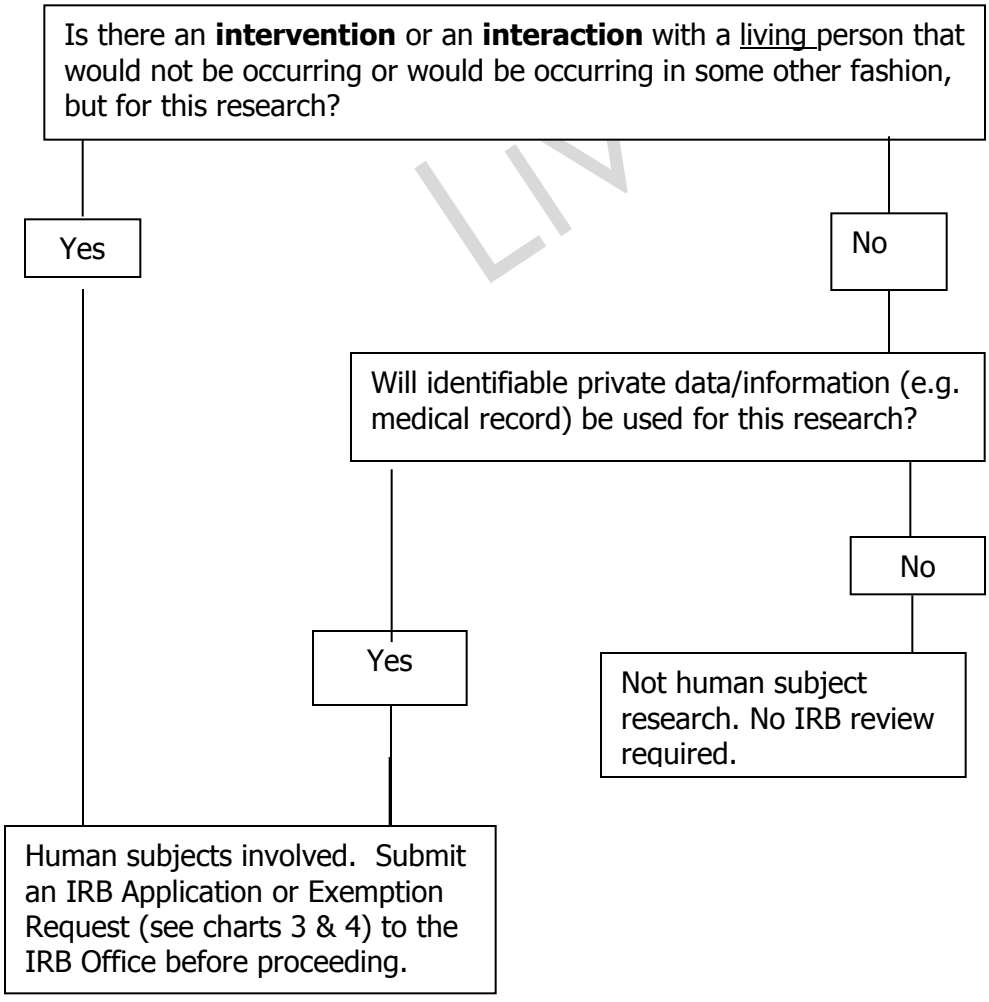


1. To contribute to "generalizable knowledge", information gathered and analyzed normally needs to be disseminated via a publication or presentation to those who can use this knowledge. For this reason, feasibility studies, which are conducted to support grant/contract applications or conducted to determine the viability of conducting a study, generally do not fall within the definition of research, and therefore do not require IRB review. If, however, there is intent to publish or present information gathered during feasibility studies, prior IRB review and approval is required.

HUMAN RESEARCH SUBJECT REVIEW DECISION CHART

- **Chart 2: Definition of "human subject"**

- The purpose of this chart is to determine if the definition of "human subject" is met in your proposed research activity?

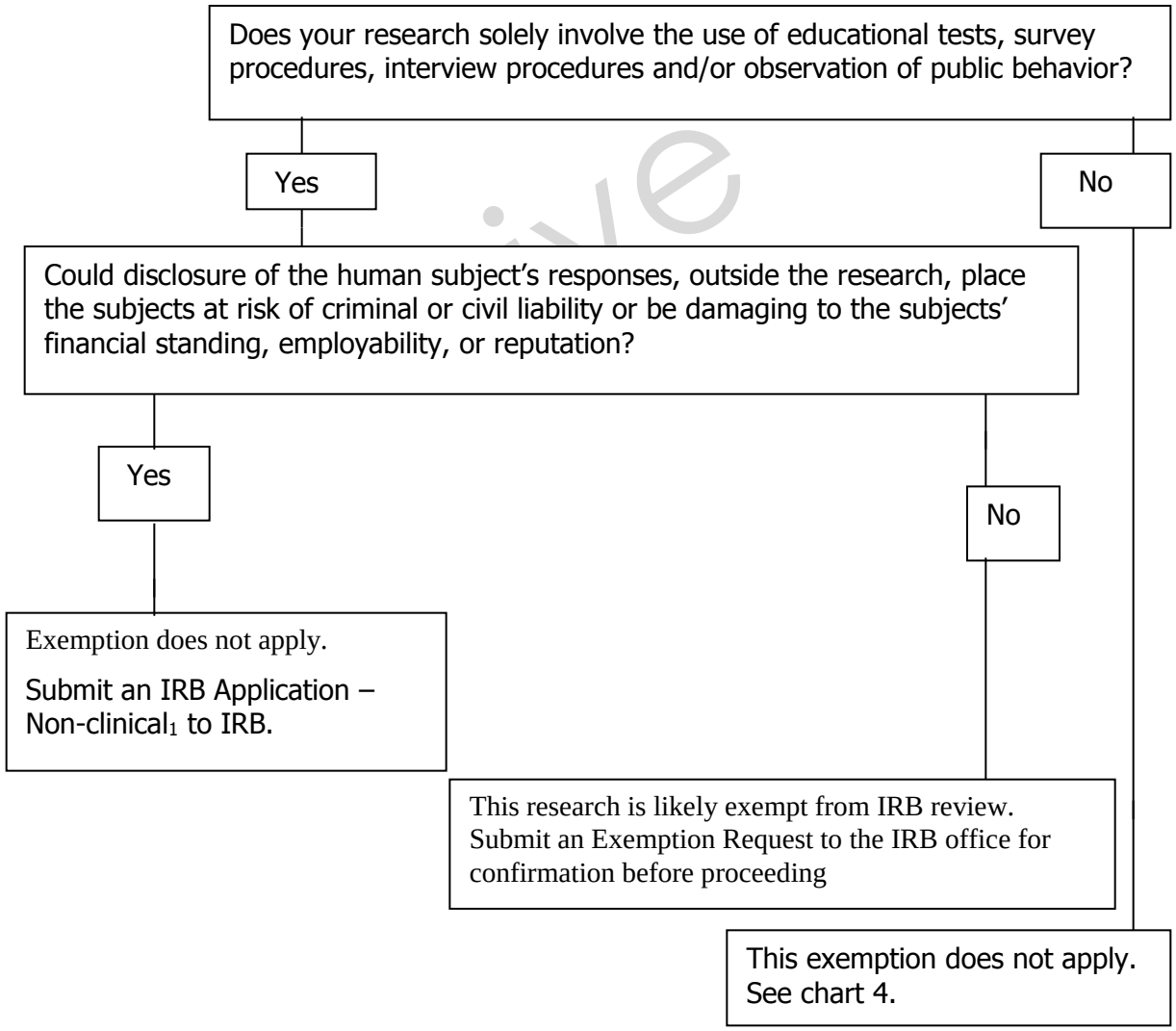


1. Available electronically from the Marshfield Clinic Intranet in the Clinic's Handbook and Policy Library, Forms Library.
2. Available electronically from the Marshfield Clinic Intranet in the Clinic's Handbook and Policy Library, Forms Library.

EXEMPT RESEARCH DECISION CHART

Some "human subject" research is exempt from <u>further</u> IRB review (after an initial determination is on file in the IRB office). The purpose of charts 3 & 4 is to determine whether you should submit an IRB Application or an Exemption Request o the IRB office.

- **Chart 3: Exemption at CFR 46.101 (b) (2)** regarding research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior.



1. Available electronically from the Marshfield Clinic Intranet in the Clinic's Handbook and Policy Library, Forms Library.
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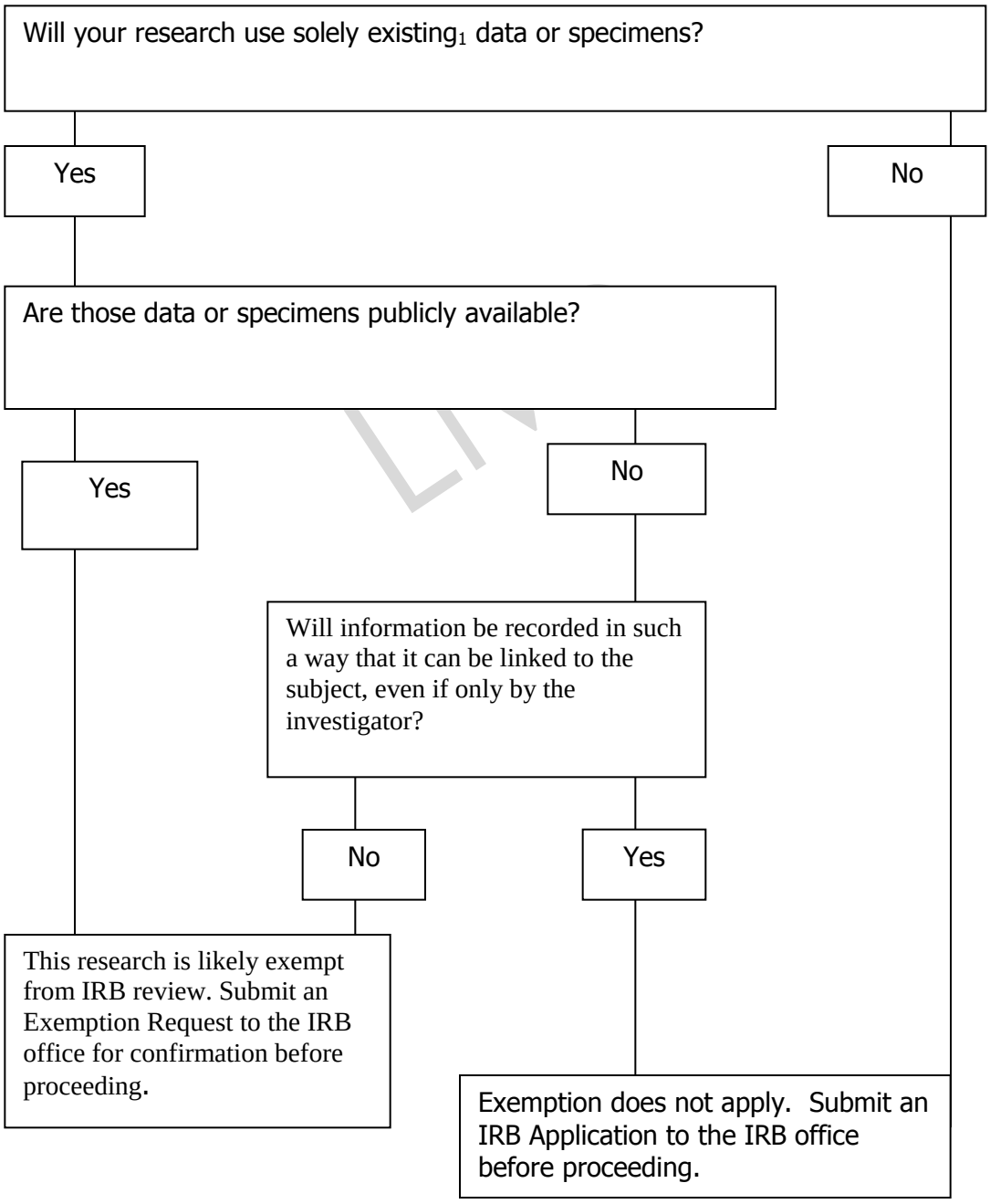
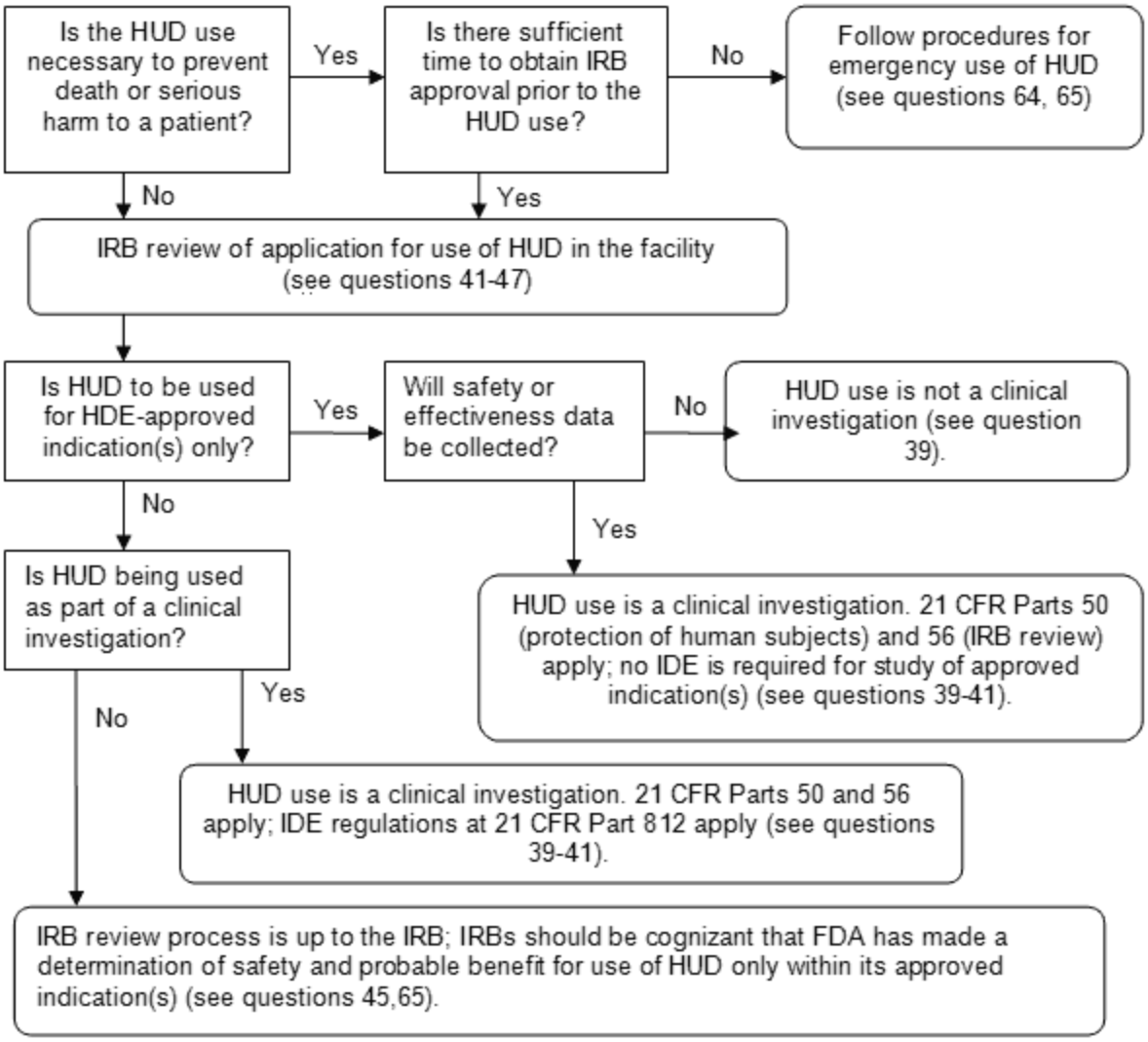
EXEMPT RESEARCH DECISION CHART (continued)

- **Chart 4: Exemption at CFR 46.101 (b) (4)** regarding research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens.



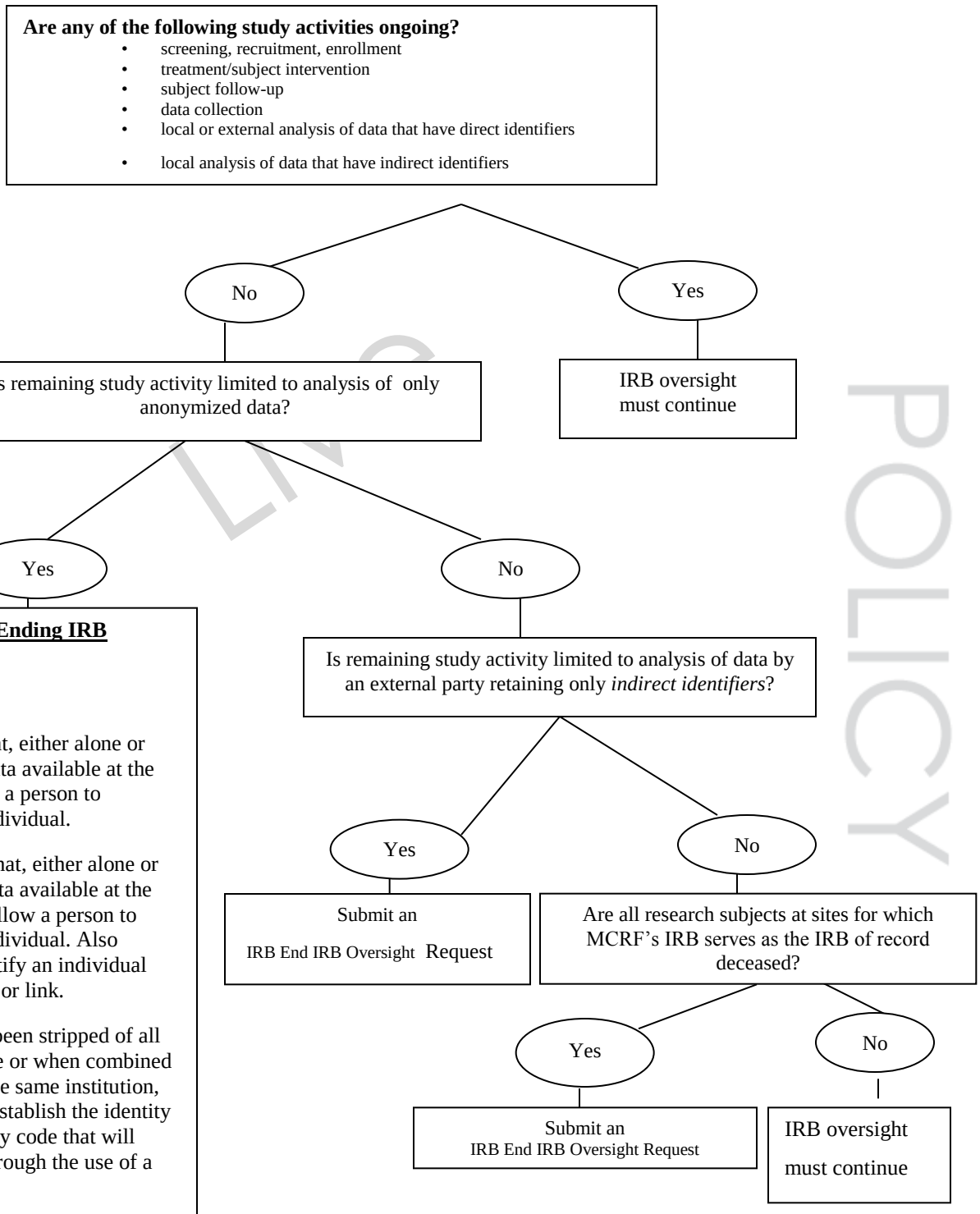
1. "Existing" means collected (i.e., on the shelf) prior to the start of the research for a purpose other than the proposed research. It includes data or specimens collected in research and non-research activities.
2. Available electronically from the Marshfield Clinic Intranet in the Clinic's Handbook and Policy Library, Forms Library.
3. Available electronically from the Marshfield Clinic Intranet in the Clinic's Handbook and Policy Library, Forms Library.

Figure 1: Decision Tree for IRB Review of HUDs (diagram copied from CFR, please disregard references to see questions…)



Note: Medical device reporting is required under 21 CFR Part 803 whenever the use of a HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. For investigational use of a HUD under an IDE, reports of unanticipated adverse device effects must be reported under 21 CFR 812.150(a)(1) and 812.150(b)(1).

Can IRB Oversight of My Study End?



Definitions for purposes of Ending IRB

Oversight of a study

Direct Identifier: any data that, either alone or when combined with other data available at the same institution, would allow a person to establish the identity of an individual.

Indirect Identifier: any data that, either alone or when combines with other data available at the same institution, would **not** allow a person to establish the identity of an individual. Also includes a code that will identify an individual only through the use of a key or link.

Anonymized: Data that have been stripped of all identifiers and, either or alone or when combined with other data available at the same institution, would not allow a person to establish the identity of an individual, including any code that will identify an individual only through the use of a key or link.

5. ADDITIONAL RESOURCES

5.1 References:

- Decision Charts – section 4 of this document.

5.2 Supporting documents available:

- Case Reports
- Exempt Projects, Review of
- Expanded Access to Investigational Drugs or Biologics
- Humanitarian Use Device (HUD)
- Program Evaluation including Quality Assurance and Quality Improvement
  Determining the Need for IRB Review
- Ending IRB Oversight

6. DOCUMENT HISTORY

Version No.	
1.0	New Document in Document Control System transferred from Policy & Handbook Library - #790.25. Update title of Non-Compliance procedure. Remove reference that Chair for RC and IRB are the same individuals. Remove reference to Director of ORIP who is no longer at this institution. Add 3.3.a bullet point for laboratory-based human subjects research. Add 3.2.i Research QI and best practices are focus of QA & Compliance Specialist.
2.0	Add hyperlink to other referenced policies within document
3.0	3.9.a. add RCO and remove reference to ORIP; replace in 3.8.a RCO title for Director of ORIP; replace in 3.2.i with Research Compliance Educator (new title& role responsibilities); replace ORIP with Office of Research Compliance. Add Decision Charts
4.0	2.9 revised wording of definition to be consistent with other policy definitions. 3.2. b delete typo, 3.3.b change title of form referenced, 3.9 fix typo error, 4. Fix formatting within decision charts

7. DOCUMENT PROPERTIES

Primary Author: Scheller, Lori A
Co-Author(s):
Approver(s): This document has been electronically signed and approved by: Ziemba, Steven J PHD on: 4/8/2016 4:52:43 PM