Institutional Review Board Guidelines

for

Research on Human Participants

at

Gundersen Clinic, Ltd.

and

Gundersen Lutheran Medical Center, Inc.

Approved 2003

Revised 2013

Table of Contents

I. Introduction 4

II. Philosophy 5

III. Definitions 6

IV. HSC Membership and Structure 8

V. Functions and Responsibilities of the Human Subjects Committee 10

VI. IRB Procedure for Consideration of Protocols 12

VII. Protocol Review Guidelines 14

Protocols That May Be Exempt From HSC/IRB Approval 14

Procedure for Expedited Review Of Protocol 15

Procedure for Full Review Of Protocols 15

Procedure for Determining Risk in Medical Device Studies l8

VIII. Procedure for Approval of Protocol Modification 20

Required Reporting 20

Procedure for Expedited and Full HSC/IRB Review of Progress and Final Reports 20

Procedure for Review of Safety Reports 21

IX. Procedure for Single Use of a Test Article 23

Emergency use 23

Treatment use of investigational test articles **23**

Compassionate Use **24**

X. Guidelines for Informed Consent **25**

XI. Misconduct in Science **28**

APPENDIX A: Application for IRB Review / IRB Questionnaire **30**

APPENDIX B: Application for HIPAA Waiver **35**

APPENDIX C: Research Committee Reviewer Checklist **38**

APPENDIX D: HSC/IRB Reviewer Checklist **40**

APPENDIX E: HIPAA Checklist **42**

APPENDIX F: Sample Consent Form and Template **45**

APPENDIX G: Guidelines for Preparing a Prospective Research Study Protocol **51**

APPENDIX H: IRB Progress/Final Report Form **55**

APPENDIX I: Progress Report for Approved HIPAA Waivers **58**

APPENDIX J: Non-employee Researchers **60**

APPENDIX K: Sample Data Use Agreement **63**

APPENDIX L: Protocol Violations and Deviations **69**

I. Introduction

Since 1974 federal law has required that a committee exist at every institution conducting research on human participants that is funded by the Department of Health and Human Services (DHHS). An Institutional Review Board (IRB) at Gundersen Clinic, Ltd. (GC) and Lutheran Hospital-La Crosse was formed in response to those requirements of federal law on January 2, 1976. This IRB is called the Human Subjects Committee (HSC).

The HSC/IRB reviews all research or use of experimental treatments involving human participants for scientific and ethical merit regardless of the source of funding. The HSC/IRB functions to comply with the regulations established by the DHHS, the Federal Drug Administration (FDA), and the Health Insurance Portability and Accountability Act (HIPAA). These regulations are only applicable to research that involves intervention or interaction with human participants or identifiable, confidential information of individual persons.

In order to clarify its position in relation to GC and Gundersen Lutheran Medical Center (GLMC) and to publish the procedures followed by it, the HSC/IRB approved the following statements in 2003. They state the official philosophy, procedures, functions, responsibilities, and membership of the HSC/IRB, which adhere to the Code of Federal Regulations (CFR) revised effective April 10, 1998, as defined by the DHHS in 45 CFR Part 46, by the FDA in 21 CFR parts 50 and 56, and by HIPAA in 45 CFR parts 160 and 164 revised March 27, 2002.

The HSC is the IRB for Gundersen Clinic, Ltd. The Committee has a Federal Wide Assurance for the Clinic, FWA00001183. This Committee also serves as the IRB for GLMC, which defers review and oversight to the HSC as indicated in the Federal Wide Assurance for the Medical Center. The Federal Wide Assurance # for the Medical Center is FWA00001305.

All researchers conducting research at Gundersen Health System must abide by Gundersen Policies GL-5805 and HR-205 to ensure protection of patient confidentiality.

II. Philosophy

The HSC/IRB affirms the dignity of all people. We affirm that each person has a right to quality healthcare and a right to choose to participate or not participate in the health service available. We affirm that a person has the right to know about the potential risks, benefits, and other effects which accompany research before giving consent to participate in an experiment. We affirm that each person has a right to quality healthcare whether or not he/she chooses to begin or to continue participation in an experiment or research.

The HSC/IRB's primary concern is safeguarding the rights and welfare of fellow human beings as they are involved in research projects and experiments.

The HSC/IRB endorses the ethical principles concerning the exercise of caution by researchers in human experimentation, as set forth in the Declaration of Helsinki, The Belmont Report, and Guideline for Good Clinical Practice as developed by the International Conference on Harmonization. The World Medical Association also adopted these principles in 1964. Copies of these materials are available on request from the Chair of the HSC/IRB.

III. Definitions

Clinical Investigation: A research study involving 1 or more human participants that is carried out in a clinical setting (see "Research").

Compensation: Payment or medical care provided to participants injured in research. Does not refer to payment (remuneration) for participation in research.

Confidentiality: Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding or the original disclosure (see "Private Information").

De-identification of Protected Health Information: Health information that does not identify an individual and with respect to which there is not reasonable basis to believe that the information can be used to identify an individual as specified in 45 CFR 164.514(b)(2)(i).

Experimental: A term often used to denote a therapy (drug, device, or procedure) that is unproven or scientifically invalidated with respect to safety and efficacy. A procedure may be considered "experimental" without necessarily being part of a formal research study to evaluate its usefulness (see "Research").

Expedited Review: A review by the Chair of the HSC/IRB or a member designated by the Chair (rather than the entire HSC/IRB) of protocols that involve no more than minimal risk to the participants or amendments to protocols that are minor.

Full Review: A review by the full HSC/IRB after approval by the Research Committee.

Human Participant: A living individual about whom an investigator (whether professional or student) conducting research obtains (a) data through intervention or interaction with the individual or (b) identifiable private information (see "Private Information").

Human Subjects Committee: The name of the Gundersen Clinic, Ltd. Institutional Review Board.

Individually Identifiable Health Information: Information that is a subset of health information, including demographic information collected from an individual, and is created or received by a healthcare provider, health plan, or healthcare clearing house; and relates to the past, present, or future physical or mental health or condition of an individual.

Informed Consent: A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure.

Interaction: Interaction includes communication or interpersonal contact between investigator and participant.

Intervention: Intervention includes both physical procedures by which data are gathered, eg, venipuncture, and manipulations of the participant or the participant's environment that are performed for research

purposes.

Investigational Device Exemption (IDE): An exemption from certain rules found in the Medical Device Amendments, allowing use of not-yet-approved devices in clinical investigations.

Investigational New Drug (IND): A drug permitted by the FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and thus not yet licensed for marketing.

Institutional Review Board (IRB): Institutional Review Board is established in accord with the Federal Register for the purpose of providing protection of human participants in research studies (see "Human Subjects Committee").

Limited Data Set: Protected health information that excludes direct identifiers of the individual or relatives, employers, or household members of the individual in accordance with 45 CFR 164.514(e).

Minimal Risk: The risks of harm anticipated in the proposed research are not greater, considering the probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests.

Private Information: Confidential information whose unauthorized disclosure could violate a participant's right to privacy (see "Human Participant").

Protected Health Information: Individually identifiable health information transmitted or maintained in any medium. It excludes information in education records or employer records.

Research: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Research Committee: A Committee that primarily reviews research proposals for scientific merit, research design, conceivable risks and benefits, and requested funding. This Committee provides expert advice on these issues to the HSC/IRB.

Therapeutic Research: Research involving an intervention that has the likelihood of providing a therapeutic, diagnostic, or preventive benefit to the participants.

IV. HSC Membership and Structure

The purpose of the HSC/IRB is to ensure that the rights and welfare of human participants are protected in matters of research and experimentation conducted within GC/GLMC.

1. Qualifications for HSC/IRB members:

   A. The members shall have varying backgrounds to ensure complete and adequate review of activities commonly conducted.
   B. The HSC/IRB should be sufficiently qualified through the maturity, experience, and expertise of its members, as well as through the diversity of its membership, to assure respect for its advice and counsel for safeguarding the rights and welfare of human participants.
   C. In addition to possessing the professional competence necessary to review specific activities, the board must be able to ascertain the acceptability of proposals in terms of organizational commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes and values.
   D. The following information shall be sent to the DHHS and the FDA concerning each of the members of the HSC/IRB:
      (1) Name:
      (2) Education:
      (3) Position or occupation:
      (4) Employment or other relationship to Gundersen Lutheran Medical Center, Inc. and Gundersen Clinic, Ltd:
      (5) Experience indicating potential contributions to subcommittee deliberations:
   E. Changes in board membership shall be reported to the DHHS and the FDA in such forms and at such times as required.
   F. Names of potential members will be recommended to the CEO of Gundersen Health System for approval and appointment.
   G. The members of the HSC/IRB serve voluntarily and without recompense.
   H. A board member may be removed from the board upon missing 3 scheduled meetings in 1 year without an excuse or missing over half the scheduled meetings in 1 year. The vote by the board required for that removal shall be two thirds of the board members present.
   I. The HSC/IRB may not have a member participate in the HSC/IRB's initial or continuing review of any project in which the member has any conflicting interest except to provide information requested by the HSC/IRB. Conflicting interests include a personal involvement in the research or experiment as well as a direct financial interest in the outcome of the research including holding stock, stock options, or ownership in the company sponsoring the research or having received financial compensation from the sponsoring company for consultation, presentations, or other type of work.
   J. All members of the HSC/IRB must complete the NIH's Ethics Training for IRB members. Opportunities for attending a national IRB conference will be provided to IRB members.
2. The structure of the HSC/IRB and Research Committee.

   A. The HSC/IRB considers the ethical and human values of human research, including risks and benefits of protocols, confidentiality, informed consent, and equal access to research protocols to all qualified potential participants.
      (1) The HSC/IRB shall be composed of 7 members appointed by the CEO of Gundersen Health System,

Inc., based on a recommendation from the members of the HSC/IRB or the Research Committee.

(2) The HSC/IRB shall consist neither of a majority of members of a single professional group, nor a majority of employees of GC/GLMC, nor entirely of men or women. At least 2 members who are not employees may not have a close family member who is an employee of GC/GLMC. Alternative members may also be named for both employee and non-employee members.

(3) One of the employee members of the HSC/IRB will be an M.D. from the Research Committee. The Research Committee may nominate this person along with alternates from the Research Committee.

(4) Members serve a 1-year term that may be renewed with the approval of the CEO of Gundersen Health System.

(5) A quorum for the conduct of business is a simple majority of membership, but the M.D. member and at least 1 member whose primary concerns are in a nonscientific area must be present at all meetings.

(6) The HSC will meet at least once each month, usually on the 4th Wednesday; additional meetings will be scheduled as necessary.

B. The Research Committee (RC) will provide expert advice on newly submitted protocols that have more than minimal risk and on other research issues requested by the HSC/IRB. The RC will review research proposals for scientific merit, research design, conceivable risks and benefits, and requested funding. Protocols from national, cooperative cancer groups may be sent to the HSC/IRB with the recommendation of the cancer therapeutics committee and the approval of the Director of Research. (These national, cooperative studies will not have an RC Reviewer's Checklist.)

(1) The RC consists of the Director of Research and 10-12 committee members appointed by the Board of Trustees of the Gundersen Medical Foundation. Membership will consist of a diverse expertise in science and medicine.

(2) Members serve a 3-year term and may be renewed. One third of all members shall be appointed each year.

(3) A quorum of the RC for the conduct of business is composed of 7 members of the committee, including the chair or acting chair.

(4) The RC usually meets twice each month.

(5) Standing subcommittee:
Academic Liaison and Appeals subcommittee will be appointed by the chair to determine if sufficient changes in a rejected proposal have been made to warrant reconsideration by the full committee.

V. Functions and Responsibilities of the Human Subjects Committee

1. The HSC/IRB shall be informed about, make recommendations regarding, and approve or veto research projects or treatments that are experimental under the direction or control of GC/GLMC and their employees that involve human participants.

2. The HSC/IRB shall serve as an ethical review board for investigations or experiments involving human participants to ensure that:
   A. The rights and welfare of participants at risk are protected.
   B. Participation in human research/experimentation is voluntary.
   C. Any inducement to participation will not cloud a participant's judgment.
   D. The possible risks are minimized to the extent possible.
   E. The knowledge to be gained by the research project may benefit the participant or persons in the future.
   F. The informed consent of participants is obtained in accordance with published guidelines and regulations of the DHHS and the FDA.
   G. Confidentiality and privacy are maintained compliant with HIPAA regulations and to the extent allowed by law.
   H. All potential participants are treated fairly and equally.

3. The HSC/IRB shall develop a procedure to ensure that:
   A. All proposals for research or experiments on human participants are reviewed by the HSC.
   B. Emergency treatment using experimental methods, drugs or devices on a patient shall be reported within 5 working days to the Chair of the HSC/IRB.
   C. Proposed changes in the project must be reported and approved by the HSC/IRB prior to their implementation.
   D. Any unanticipated problems involving risks to participants or others must be promptly reported to the HSC/IRB. Any such problems, including adverse reactions to biological drugs, radioisotope labeled drugs, or to medical devices must also be promptly reported to the DHHS, the FDA and/or other agencies or organizations.
   E. A project that is approved is reviewed no less than annually, and at the termination of the research project. The need for more frequent review, based on greater risk to the participant, will be assessed at the time of initial review. The investigator will be notified of this need in the letter of approval. The HSC/IRB should determine which projects need verification from sources other than the investigator to ensure no changes in the protocol have taken place.
   F. All research conducted in cooperation with another institution shall have adequate review by this institution.
   G. All records regarding a study are kept for 3 years after the close of a study.

4. Investigators and officials at GL will be notified in writing of the HSC/IRB's decisions to approve or disapprove the proposed activity and/or of modifications required.

5. All findings and actions taken on initial or continuing review of protocols will be appropriately documented in the committee minutes and a copy will be sent to the institution officials at GL**.**

6. No other bodies within the institutions have the power to change or modify the negative decisions of the

full HSC/IRB. The researcher and institution are bound by any decisions of the HSC/IRB regarding changes in design of the protocol.

VI. IRB Procedure for Consideration of Protocols

1. The following criteria are used for protocol review:
   A. Risks to participants are minimized.
   B. Risks to participants are reasonable in relation to anticipated benefits.
   C. Selection of participants is equitable.
   D. Informed consent will be obtained prior to enrollment.
   E. Informed consent will be appropriately documented.
   F. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants.
   G. All researchers involved with the protocol have provided evidence that they have completed the NIH research ethics training or other sanctioned research ethics education.
   H. Where appropriate, there are adequate provisions to protect the privacy of participants and maintain the confidentiality of data. Where some or all of the participants are likely to be vulnerable to coercion or undue influence (such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged) appropriate additional safeguards have been included in the study to protect the rights and welfare of these participants.
   I. All potential conflicts of interest of the principal investigators have been disclosed and reviewed so that no concerns exist that the conflict will compromise the study or the rights and safety of any participant.

2. For approval, research must also meet HIPAA regulations. Approval may be given to researchers to use protected information without participants' informed consent if:
   A. the information involves only decedents;
   B. the information is being reviewed in preparation for research (see Gundersen Health System's Policy and Procedure manual, GL-5805 for more information); or
   C. the HSC/IRB has given a waiver. A waiver will be granted if:
      (1) use of protected health information involves not more than minimal risks to individuals and includes:
         a. an adequate plan to protect the identifiers from improper use and disclosure;
         b. an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification of retaining the identifiers, or such retention is otherwise required by law; and
         c. adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity except as required by law.
      (2) the research could not practicably be conducted without the waiver;
      (3) the research could not be practicably conducted without access to and use of protected health information.

   When a waiver is granted, it will also be determined by the HSC/IRB what is the minimum necessary health information that will be released to achieve the purpose of the research and how to account for access to the protected health information. If the researcher will access 49 or fewer different patients' charts, the researcher will be required to provide written evidence in the participants' charts about why, when, and by whom the charts were viewed for research.

3. All researchers must notify and briefly describe their research to the IRB Coordinator or the Chair of the

HSC/IRB before participants are identified or data collected.

4. Upon notification of a proposed research project, the Chair of the HSC/IRB must determine if a review is necessary, and if so, whether it will require a full or expedited review. Expedited review and full review require the investigator to submit a research proposal (see "Guidelines for Preparing a Protocol") and the IRB questionnaire. The HSC/IRB reserves the right to review all research involving human participants to determine the level of risk to human participants including both patients and employees of GC/GLMC.

5. Anyone on the RC or HSC/IRB who may have a financial conflict of interest in approving or disapproving a research protocol or experimental treatment must disclose this conflict to the Chair of the respective Committee and abstain from voting.

VII. Protocol Review Guidelines

Protocols That May Be Exempt From HSC/IRB Approval

The following types of research may be exempt from review by the HSC/IRB because they represent no risk to the participant. The HSC/IRB retains final judgment as to whether a particular activity is covered by this policy. To determine if a research project does not need HSC/IRB approval, please contact the Chair of the HSC/IRB.

1. Educational Practices: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (1) research on regular and special education instructional strategies, or (2) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Survey, Interview, and Observation Research: All research involving solely the use of survey or interview procedures or observation, including observation of participants' public behavior, is exempt unless:
   A. the responses are recorded in a manner such that the participants can be identified either directly or through identifiers linked to them, or
   B. the participants would be at risk of (a) criminal or civil liability or (b) damage to financial standing or (c) damage to employability if the responses become known outside the research, or
   C. the research deals with sensitive aspects of the participants' behavior, eg, illegal conduct, drug use, sexual behavior, use of alcohol, or
   D. more than a brief amount of time is needed from participants, including a survey repeated over time.

3. Educational Tests: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), if information taken from these sources is recorded in such a manner that participants cannot be identified, directly or through identifiers linked to the participants.

4. Quality improvement projects: These projects include the collecting of information or data in a systematic way to improve the practice and care of patients within Gundersen Lutheran Medical Center, Inc. or Gundersen Clinic, Ltd. These projects are intended to improve operations, but not to add to generalizable knowledge. Typically, quality improvement projects are not rigorous in methodology and design, are not intended to be published, and will not be adequate to answer important questions of interest to a discipline or profession.

5. Research where all identifiers have been removed from existing protected health information as specified in 45 CFR 164.514 (b)(1) or (2).

6. Research where a limited data set, as defined in 45 CFR 164.514 (e) (2), will be used and the researcher has entered into a data use agreement with Gundersen Clinic, Ltd. or Gundersen Lutheran Medical Center. See Appendix K for a sample of the data use agreement.

Procedure For Expedited Review Of Protocol

1. Expedited review can be done for certain kinds of research involving no more than minimal risk, for minor changes in approved research, and for review of ongoing research that has no more than minimal risk.

2. Review is conducted at least once a month by the chair of the HSC/IRB or a member designated by the HSC/IRB chair. If the HSC/IRB member doing the review needs additional advice from another HSC/IRB member, such consultation will be sought and the minutes will reflect the involvement of this additional HSC/IRB member. The reviewer will complete a review checklist for each new protocol reviewed.

3. The researcher may be invited to provide additional information in person.

4. The Chair of the HSC/IRB shall send a letter to the researcher advising him or her of the decision.

5. Results of the decision of the expedited review shall be reported in minutes to the full HSC/IRB.

6. Under expedited review, unapproved protocols may be submitted for full review.

Procedure For Full Review Of Protocols

1. Two copies of both a new research protocol and the IRB questionnaire meeting the requirements set forth in Appendices A, C, and D, plus a copy of the Investigator's Brochure (when available), should be submitted to the IRB Coordinator.

2. The RC Chair will establish the review process needed for the protocol. This may include selecting at least 2 reviewers for each protocol. One reviewer will have a copy of the Investigator's Brochure (when available). Each primary reviewer will complete the RC Reviewer's Checklist. The reviewers will present and analyze the protocol at the full committee meeting and make appropriate motions for disposition of the protocol. The reviewers may contact the investigator in advance of the meeting for explanation or clarification of points that may bear adversely on acceptance of the protocol or to request missing material. All members of the RC may take the opportunity to review a proposal before the members are requested to vote on a proposal. An investigator is entitled to appear before the RC to explain a protocol. Voting shall be by voice unless any member requests a secret ballot. A protocol can be approved only if it receives a majority of votes. The IRB Coordinator will record the vote. Justifications for changes in a protocol or disapproval of research must be included in the minutes.

3. At its discretion, the RC may invite individuals or committees with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on

the RC.

4. Rejected proposals may be resubmitted for review if the Academic Liaison and Appeals standing committee decides sufficient changes have been made in the original proposal to warrant reconsideration.

5. When a proposal is approved with modifications, limitations, or conditions, a copy of the revised protocol must be submitted to the IRB Coordinator.

6. The Chair of the RC will send a letter to the researcher and the HSC/IRB advising them of the decision.

7. If the proposal is approved by the RC, the proposal will be forwarded to the HSC/IRB.

8. For a research proposal to be considered at an HSC/IRB meeting, all members of the HSC/IRB shall have a completed copy of the IRB Questionnaire, an abstract/summary of the research project, the RC Reviewer's Checklist, and the consent form at least 3 days before the meeting.

9. The Chair of the HSC/IRB will select 1 reviewer for each protocol. The reviewer will also have the full protocol and the Investigator's Brochure. The reviewer will complete the HSC/IRB Reviewer's Checklist. The reviewer will present and analyze the protocol at the full HSC/IRB meeting and make appropriate motions for disposition of the protocol, with re-review at least annually unless the reviewer recommends a more frequent interval. The reviewers may contact the investigator in advance of the meeting to explain or clarify points that may bear adversely on acceptance of the protocol. All members of the HSC/IRB have the opportunity to review a proposal before the members are requested to vote on a proposal. An investigator is entitled to appear before the HSC/IRB to defend a protocol. Voting shall be by voice unless any member requests a secret ballot. To be approved, any motion must have the majority approval of members present. The IRB Coordinator will record the vote by indicating the number of votes for, against, or abstaining. Justifications for changes in a protocol or disapproval of research must be included in the minutes along with discussion of controverted issues and their resolution.

10. The HSC/IRB, at its discretion, may invite individuals or committees with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the HSC/IRB.

11. Any member of the HSC/IRB may request that the Committee discuss a motion in closed session. This request may be made during the meeting or may be communicated to the Chair before the meeting begins.

12. The HSC/IRB will approve or disapprove a protocol by a simple majority of those present.

13. Approval by the RC is required before a protocol can be considered by the HSC/IRB. Approval by both the RC and the HSC/IRB is required for new protocols with more than minimal risks. Any other body having power of review may reject a protocol approved by the HSC/IRB. The

HSC/IRB may disapprove or require modifications, limitations, or conditions. A negative decision of the HSC/IRB cannot be altered or modified by other individuals or groups at GC/GLMC. Modifications, limitations, or conditions must be included in the minutes. A copy of revisions made by the principal investigator must be submitted to the HSC/IRB before approval is given.

14. The Chair of the HSC/IRB shall send a letter to the researcher advising of the decision of the HSC/IRB.

15. When a research project has been approved, the letter shall include the requirements:
    A. that the researcher report any proposed changes in the research and any unanticipated problems involving risk to participants or others promptly to the HSC/IRB. Changes in the protocol may not be initiated without HSC/IRB approval except when necessary to eliminate apparent immediate hazards to the participant;
    B. that the researcher report any unanticipated adverse events, including adverse reaction to biological drugs, radioisotope-labeled drugs, or medical devices to the Chair of the HSC/IRB, the DHHS, and the FDA and/or other participating agencies or organizations within 5 days. If the adverse effect is serious, it must be reported to the HSC within 24 hours; and
    C. that the researcher submit to the Chair of the HSC/IRB updated progress reports of approved research to the HSC/IRB as required in the original approval and at termination of the research.

Procedure for Determining Risk in Medical Device Studies

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" *(SR)* and "non-significant risk" *(NSR)*.

The effect of the *SR*/*NSR* decision is very important to research sponsors and investigators. *SR* device studies are governed by the IDE regulations [21 CFR part 812]. *NSR* device studies have fewer regulatory controls than *SR* studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements.

For both *SR* and *NSR* device studies, Research Committee (RC)/Human Subjects Committee (HSC)/IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

Definitions:

Significant Risk Device

An *SR* device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Nonsignificant Risk Device

An *NSR* device study is one that does not meet the definition for a significant risk study. *NSR* device studies, however, should not be confused with the concept of "minimal risk," which is a term that is utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56]. *SR/NSR* determinations are separate and distinct from Greater than Minimal Risk/Not Greater than Minimal Risk determinations. For a device study to be eligible for expedited review, it must be an *NSR* device AND the research must present no greater than minimal risk to the subject [21 CFR 56.110].

Sponsor/Investigator Responsibilities:

Sponsors are responsible for making the initial risk determination and Investigators will present it to the RC and HSC/IRB as part of the IRB submission. The sponsor must provide the RC and HSC/IRB with an explanation of its *SR/NSR* determination and any other information that may help in evaluating the risk of the device. For example, the RC and HSC/IRB would need description/specifications of the device, the nature of any potential harm that could result from the use of the device in the intended population, and if available, reports of prior investigations with the device. If FDA has already determined that the device is *NSR*, the sponsor should so inform the RC and HSC/IRB.

For *SR* device studies, the sponsor must submit an IDE application to FDA and obtain the agency's approval of the study. Sponsors/Investigators must provide the IDE number and/or a copy of the IDE approval letter to the RC and HSC/IRB as part of the IRB submission.

RC and HSC/IRB Responsibilities:

Unless FDA has already made a risk determination for the device study, the RC and HSC/IRB must review the sponsor's *SR* or *NSR* determination for every investigational medical device study it reviews and modify the determination if the IRB should disagree with the sponsor. If FDA has already made the *SR/NSR* determination for the device study, the agency's determination is final. If the device already has an approved IDE, the RC and HSC/IRB will require documentation from the sponsor that the IDE number applies to the device to be used for the study under consideration. This may be reflected in the sponsor's protocol, or correspondence from the sponsor or FDA. FDA will provide a written determination of *SR/NSR* status at the request of the HSC/IRB.

The RC and HSC/IRB will make the *SR* or *NSR* determination about a device study by reviewing relevant information at convened meetings. If the RC and HSC/IRB determines the device is *NSR*, they may approve the study using the criteria at 21 CFR 56.111. In that case the study may then begin without submission of and IDE application to FDA.

If the RC or HSC/IRB disagrees with the sponsor's *NSR* assessment and decides the study is a *SR* device study, the HSC/IRB will communicate this to the investigator and where appropriate, the sponsor. The HSC/IRB may conditionally approve the study as an *SR* device study, but the study may not begin until FDA approved the sponsor's IDE application, or provides a determination that the device as proposed for use in the investigation is *NSR*.

The RC and HSC/IRB will document its *SR/NSR* determination in the meeting minutes. The IRB study file will also include, as applicable, the documentation used to establish the IDE status for the study. For an *SR* determination, such documentation is to include a copy of the IDE approval or conditional letter from FDA.

VIII. Procedure for Approval of Protocol Modification

Required Reporting

An investigator is required to report in writing to the HSC/IRB within 5 days any unanticipated adverse effects that are encountered by a participant enrolled in a protocol. If the unanticipated adverse effect is serious it must be reported to the HSC/IRB within 24 hours. Adverse events that are expected end-points should be reported as part of progress reports as needed.

Procedure for Expedited and Full HSC/IRB Review of Progress and Final Reports

In order to remain active, a protocol must be reviewed at least annually, or as recommended by the HSC/IRB. Progress and final reports are made by using the form in Appendix H.

Progress reports will receive expedited review when the research is closed to enrollment, the study is doing only long-term follow-up, no participants have been enrolled, no additional risks have been identified, or the only task that remains is data analysis. Full review will occur in all other studies.

For full review, each member of the HSC/IRB will receive a copy of the Progress/Final Report form and the abstract from the protocol. In cases where there are changes to the consent form, each member will receive a copy of the old and new consent forms. If the responses on the Progress/Final Report form indicate that a study is active with enrolled participants—and there are new risks, changes in the consent form that require approval, or other information or changes that have not been previously approved, the study will be assigned to an HSC/IRB member for re-review.

The HSC/IRB may request an update or progress review from any investigator at any time. The HSC/IRB Chair will, from time to time, conduct such additional reviews as may be necessary to assure that compliance with policies, guidelines, and pertinent law is satisfactory. If the Chair determines that new information about an approved research project or experiment raises unforeseen risks to participants, the Chair may suspend the project until these concerns have been addressed or the HSC/IRB has had an opportunity to review the new risks and provides a new approval for the project to continue.

The IRB Coordinator will issue notices to investigators that periodic review is due. Failure to provide a response to a request for update or periodic review is cause for withdrawal of approval. Approval of protocols that are not carried out within a reasonable time will be withdrawn, and such protocols will be inactivated. An investigator may resubmit an inactive protocol for approval when the study is ready to begin.

If a final report is not completed because a researcher is no longer available, the IRB Coordinator will complete a final report using the best information available.

Procedure for Review of Safety Reports

Safety reports will normally be reviewed at the regular, monthly meeting. All safety reports must be reviewed and initialed by the Principal Investigator prior to submission to the HSC/IRB. The M.D. member or another member of the HSC/IRB will review the safety reports for a meeting of the HSC/IRB. The reviewing HSC/IRB member will report on this review and be prepared to discuss the safety reports that may require reconsideration of a protocol or changes in a consent form. The safety reports will be available for review by all members of the HSC/IRB at the meeting of the Committee.

If a serious, unanticipated adverse event happens to a subject as part of study at GC/GLMC, the Director of the RC or the Chair of the HSC/IRB (or other members of these Committees) will review the report of the event within 48 hours of its receipt from the researcher.

The Gundersen Clinic HSC/IRB acknowledges and refers to the following OHRP guidance regarding time frame for submission of safety reports:

OHRP Guidance on Unanticipated Problems and Adverse Events
January 15, 2007
For multicenter research projects, only the institution at which the subject(s) experienced an adverse event determined to be an unanticipated problem (or the institution at which any other type of unanticipated problem occurred) must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.103(b)(5)). Alternatively, the central monitoring entity may be designated to submit reports of unanticipated problems to the supporting agency head (or designee) and OHRP.

V. What is the appropriate time frame for reporting unanticipated problems to the IRB, appropriate institutional officials, the department or agency head (or designee), and OHRP?
The HHS regulations at 46.103(b)(5) require written procedures for ensuring prompt reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm.

The regulations do not define prompt. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, OHRP recommends the following guidelines in order to satisfy the requirement for prompt reporting:

(1) Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.

(2) Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

(3) All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

OHRP notes that, in some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, appropriate institutional officials, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

IX. Procedure for Single Use of a Test Article

Emergency use

Federal regulations (21 CFR 50.23) provide for the emergency use of an investigational new drug (IND), biologic, or to obtain an investigational device exemption (IDE) in a life-threatening situation in which no standard acceptable treatment is available and in which there is insufficient time to obtain HSC/IRB approval. Emergency use is exempt from prior HSC/IRB review provided that such emergency use is documented in writing and sent to the IRB office within 5 working days and informed consent is obtained. If continuing use of that product for the same patient is anticipated, a protocol as well as the emergency notification should be sent to the HSC/IRB for its review and approval. Any subsequent use of the investigational product for a different patient, or for the same patient at a later date and different course of treatment, is subject to prior HSC/IRB approval.

Treatment use of investigational test articles

The FDA has a procedure under which promising investigational test articles may be made available to patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapies exist. Their intent is to make promising new drugs and test articles available to patients as early in the drug development process as possible and to obtain additional data on the drug's safety and effectiveness. A treatment protocol allows use of a promising new article directed primarily at patient care by physicians who agree to follow the protocol.

The treatment use regulations (21 CFR 312.34b) set forth criteria by which FDA evaluates whether a drug in clinical trials may be used under a treatment protocol. FDA will permit an investigational drug or article to be used for a treatment use under a treatment protocol if:

1. The drug is intended to treat a serious or immediately life-threatening disease.

2. There is no comparable or satisfactory alternative drug, article, or therapy available to treat that stage of the disease in the intended patient population.

3. The drug or article is under investigation in a controlled clinical trial, or all clinical trials have been completed.

4. The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug or article with due diligence.

To seek approval for investigational articles for 1 patient, physicians will need to submit a letter explaining the rationale for use of the investigational article for the patient and a protocol with consent form. An employee member of the HSC/IRB and the Chair of the RC or another M.D. member of the RC will approve the use of the investigational drugs or devices for the treatment for a single patient.

To seek approval for this use of investigational test articles for a number of subjects/patients, physicians will need to complete the IRB Questionnaire and provide a protocol including a consent form. This material will undergo a full review.

Compassionate Use

Although not an official category of investigational use, times may arise when an investigational drug does not strictly meet the criteria of treatment use as outlined above. For example, the company may never market certain drugs, or they may be orphaned for other reasons. If a physician wishes to pursue treatment for a serious medical condition, usually where there is no approved or generally recognized therapy, that physician may be allowed to use the drug under the sponsor or manufacturer's Investigational New Drug (IND). In the event that an IND is not in effect for that application, the physician must file a new IND.

An employee member of the HSC/IRB and the Chair of the RC or another M.D. member of the RC will approve the use of the investigational drugs or devices for "compassionate use" for a single patient. To request approval, a physician must submit a letter describing the rationale for the treatment, any protocol provided by the company, and a consent form.

X. Guidelines for Informed Consent

Investigations involving any risk to human participants require informed consent (except as provided in HIPAA) in language understandable to the proposed participants from each participant, or from a legally authorized representative of the participant. In Wisconsin, a legal authorized representative is either a legal guardian for a legal incompetent adult, a parent for a minor, or a healthcare agent for an adult who has a legally valid power of attorney for healthcare that has been activated.

When informed consent is required, it shall be obtained by use of a written consent form or orally as approved by the HSC/IRB.

When a written consent form is used, the participant or the participant's legally authorized representative must sign it. If a proposed study involving minors is determined to be more than minimal risk there should be 2 parent/legal representative signature lines on the consent form to be used if at all possible. If it is impossible to obtain the consent of both parents (1 parent is deceased, unknown, incompetent, or not reasonably available), this needs to be noted on the consent form by study staff and should be brought to the attention of the IRB. A copy of the approved form must be offered to the person signing the form and a copy must also be placed in the participant's medical record.

The clinical investigator is responsible for ensuring that informed consent is obtained from each research participant before that participant participates in the research project. Regulations do not require the investigator to personally obtain the informed consent. The investigator can ensure that an individual knowledgeable about the research presents the information to the participant, that the participant understands the information, and that the participant signs a consent form. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another.

All adults (including those with cognitive impairments) are presumed competent to consent unless legally judged to be incompetent or their medical record lists their power of attorney for health care as activated. Cognitively impaired persons are considered a vulnerable research population because their mental disability may compromise their capacity to make a reasoned decision about participation in a study. Investigators interested in enrolling individuals with cognitive impairment in research studies at Gundersen Health System are required to submit the request to the Human Subjects Committee (HSC)/IRB Chair or the Chair's representative (alternate or another member of the HSC) for review.

While there are no standardized measures for determining capacity to consent, subjects may be assessed on their ability to understand and to express a reasoned choice concerning the:

- Nature of the research and the information relevant to his/her participation;
- Consequences of participation for the subject's own situation, especially concerning the subject's health condition; and
- Consequences of the alternatives to participation.

People with Alzheimer's disease, dementia, mental illness, and developmental disabilities may be considered cognitively impaired and may not be able to provide informed consent for participation in research. In certain circumstances, when it is determined that a potential research participant is cognitively impaired, federal regulations and state statute permit researchers to obtain consent from a legally-authorized representative.

When consent will be obtained from a legally-authorized representative, the IRB will require that the assent of the subject be obtained if that is possible. Assent is defined as affirmative agreement to participate in research. Failure to object does not qualify as assent.

If subjects are 14-18 years of age, assent must be obtained. If subjects are 7-13 years of age, the HSC/IRB will determine if assent is needed. Assent is not needed for subjects who are younger than 7 years old.

When the HSC/IRB requires a written consent form that will be signed by the participant, the HSC/IRB will determine if a witness or witnesses are needed. Generally, when the study or project involves only minimal risk only 1 witness will be needed. The witness may be an employee, a family member, or a volunteer, but not the researcher obtaining consent.

The basic elements of informed consent are:

1. A statement that the study involves research, why the study is being conducted, the expected duration of the participant’s participation and the reason the participant was selected.

2. A statement giving a brief explanation of the purposes of the research.

3. A statement giving a description of the procedures to be followed, and identification of any procedures that are experimental.

4. A description of any reasonably foreseeable risks or discomforts to the participant.

5. A description of any benefits to the participant or to others that may reasonably be expected from the research.

6. A statement describing financial responsibility or compensation, if any, attributed to the participant.

7. An explanation of whom to contact (including telephone numbers) for answers to pertinent questions about the research, including the chair of the HSC/IRB for information regarding participant’s rights in research studies, and whom to contact in the event of a research-related injury to the participant.

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

9. A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained. If information will be obtained from subjects' medical records, the consent form needs to clearly indicate the following:
   A. a description of the type of information to be used and collected;
   B. the names of the persons or classes of persons authorized to obtain the information;
   C. the names of the persons or classes of persons who may look at the information;
   D. an indication for how long the information might be collected;
   E. the right of the subject to revoke access and any exceptions to revoking;
   F. how to revoke the access; and
   G. a statement that any information obtained may be subjected to redisclosure as required by law.

10. Signature of the participant (or legal representative: a parent for a minor; a legal guardian, or a healthcare agent) and the researcher obtaining consent, and (possibly) designated witnesses.

11. Other elements that may be required are:
   A. a statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus if the participant is or may become pregnant) that are currently unforeseeable.
   B. 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.
   C. a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
   D. anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent.
   E. the consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
   F. a statement that significant new findings developed during the course of the research that may relate to the participant's willingness to continue participation will be provided.

XI. Misconduct in Science

1. Definition:
   A. As defined by the Public Health Service in the Code of Federal Regulations (CFR) 42 Part 93, Final Rule on Responsibilities of Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science: "Misconduct" or "Misconduct in Science" means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. It does not include honest error or honest differences in interpretations of judgments of data.
   B. As defined by the National Science Foundation: Material failure to comply with Federal requirements for protection of researchers, human participants, or the public or for ensuring the welfare of laboratory animals, or failure to meet other material legal requirements governing research.

2. The purpose of this policy is to establish a review mechanism for all allegations of scientific misconduct, whether internal or external as required by Public Health Service 42 CFR Part 93. This will ensure that GC/GLMC:
   A. has established an administrative process, that meets the requirements of 42 CFR Part 93 for reviewing, investigating, and reporting allegations of misconduct in science; and
   B. will comply with its own administrative process and the requirements of 42 CFR Part 93.

3. Functions and Responsibilities related to compliance with 42 CFR Part 93 will be addressed by the Gundersen Clinic, Ltd. Administrator and Gundersen Lutheran Medical Center Administrator.
   A. GC/GLMC will submit annual assurances for their respective institutions to the Office of Research Integrity (ORI);
   B. establish and keep current policies and procedures required by 42 CFR Part 93;
   C. inform its scientific and administrative staff of the policies and procedures and the importance of compliance with those policies and procedures;
   D. take immediate and appropriate action as soon as misconduct on the part of employees or persons within the organization's control is suspected or alleged; and
   E. inform and cooperate with the ORI with regard to each investigation of possible misconduct.

4. GC/GLMC will follow the policies and procedures outlined below when inquiring, investigating, and reporting incidence of misconduct in science:
   A. The allegations of possible misconduct must be made in writing to the Director of Research. The written report will be held highly confidential to protect the parties involved.
   B. GC/GLMC shall inquire immediately into an allegation or other evidence of possible misconduct. An internal review committee shall be established by the Director of Research to review any allegations of scientific misconduct. This standing committee, the Misconduct in Science Committee (MSC), will consist of the Chair of each of the standing committees of the Research Subcommittee and the Chair of the HSC/IRB. This inquiry must be completed within 60 calendar days of its initiation unless circumstances clearly warrant a longer period. A written report will be prepared that states what evidence was reviewed, summarizes relevant interviews, and includes the conclusions of the inquiry. The individual(s) against whom the allegation was made shall be given a copy of the report of inquiry. If they comment on that report, their comments shall be made part of the record. If the inquiry takes longer than 60 days to complete, the record of the inquiry shall include documentation of the reasons for exceeding the 60-day period.
   C. GC/GLMC and the MSC shall protect, to the maximum extent possible, the privacy of those who in good faith report apparent misconduct.
   D. The MSC will afford the affected individual(s) confidential treatment to the maximum extent possible, a prompt and thorough investigation, and an opportunity to comment on allegations and findings of the inquiry and/or the investigation.
   E. The staff of the Grants Management Office shall notify the Director of the ORI in accordance with Section 93.309 when, on the basis of the initial inquiry, the MSC determines that an investigation is warranted, or prior to the decision to initiate an investigation if the conditions listed below exist:
      (1) there is an immediate health hazard involved;
      (2) there is an immediate need to protect Federal funds or equipment; or
      (3) there is an immediate need to protect the interests of the person(s) making the allegations or the individual(s) who is the participant of the allegations as well as his/her co-investigators and associates, if any.

APPENDIX A: Application for IRB Review / IRB Questionnaire

IRB Questionnaire

Gundersen Clinic, Ltd.
Human Subjects Committee/IRB

IRB #: _____

Date Approved: _____

-For Office Use Only-

In addition to two copies of a complete protocol, this **COMPLETED, PRINTED** form is required for review. **If you need additional space for any response, please attach a Word document.**

Date Submitted:

Principal Investigator: Telephone:

Email:

Co-Investigators:

Coordinator: Telephone:

Study Title:

Cooperative or Company number (if appropriate):

Source of Funding:

Expected Number of Subjects: Local: National:

Duration of Data Gathering: From: To:

Expected Date of Completion of Project:

Does the protocol include:

Children (younger than 18 years of age)? Yes No

--If yes, ages are

Pregnant women? Yes No

Investigational devices? Yes No

--If yes, who is the manufacturer or sponsor?

--Will you need to obtain an IDE application? (Investigational Device Exemption) ☐ Yes ☐ No

Investigational Drugs?** ☐ Yes ☐ No
--If yes, who is the manufacturer or sponsor?

--Will you need to obtain an IND application? (Investigational New Drug) ☐ Yes ☐ No

**If answered YES, I agree that any investigational drugs involved in this protocol will be kept in a locked repository.

1. Assuming that "risk" is defined as danger to the subject above and beyond that to which he/she is already being exposed as a patient or as a normal healthy person, how much risk is involved for the subjects in this study?

☐ Large ☐ Moderate ☐ Some ☐ Very little ☐ None

2. How much personal discomfort or disruption of normal activities may the subjects in the study experience?

☐ Large ☐ Moderate ☐ Some ☐ Very little ☐ None

3. If successful, do you think that the research will provide any long- or short-term benefits for the subjects or for others?

For Subject: ☐ Great ☐ Moderate ☐ Some ☐ Little ☐ None

For Others: ☐ Great ☐ Moderate ☐ Some ☐ Little ☐ None

4. In your estimation, how significant for the advancement of knowledge is this research?

☐ Outstanding ☐ Significant ☐ Greater than Average ☐ Interesting

5. Will subjects receive any remuneration? ☐ Yes ☐ No

6. Does the study require any extra procedures, laboratory tests, or any other costs to the subjects that are not required for therapy alone? ☐ Yes ☐ No
--If your answer is yes, please describe:

7. Will any of the investigators receive any direct compensation from sources other than Gundersen Health System for conducting this study? Yes No
   --If your answer is yes, please explain:

8. To your knowledge do you or does anyone in your immediate family own any stock or have any financial interest in the drug/device sponsor? Yes No
   --If your answer is yes, please explain:

9. Do you have any financial, consulting, or other arrangement with the company sponsoring the research? Yes No
   --If your answer is yes, please explain:

10. Do you have or claim any intellectual property rights in the drugs or medical devices that are the subject matter in the study? Yes No
    --If your answer is yes, please explain:

11. Do you have any financial relationships noted on your Gundersen Health System Conflict of Interest Disclosure Statement related to this research protocol? Yes No
    --If your answer is yes, please attach a copy of the disclosure statement.

12. Have the personnel conducting the study and obtaining consent completed the Gundersen Clinic, Ltd. HSC required ethics education program? (may be accessed at http://phrp.nihtraining.com) Yes No

13. Describe who will obtain consent, when, where, and how:

14. Have all clinic/hospital departments directly involved in the care of patients for this protocol been apprised of this study? ☐ Yes ☐ No

15. Is this an infusion study or a hospital-based drug study? ☐ Yes ☐ No

--If your answer is yes, has the hospital pharmacy department agreed that it can provide the necessary resources? ☐ Yes ☐ No

16. Does at least two thirds of your department or section agree that this protocol is acceptable? ☐ Yes ☐ No

17. In addition to the completion of this questionnaire, you must also submit:
    A. A brief abstract describing the study;
    B. Letters of support from any cooperating departments;
    C. Two copies of the complete protocol that include:
        (1) hypothesis to be tested
        (2) background information
        (3) study design
        (4) methods to be used for analysis
        (5) itemized and total budget
        (6) consent form (if needed)
        (7) bibliography
        (8) likely place/location of personnel, supply storage, and data storage

I request IRB review of this study and, if approved, I accept responsibility for conducting the study in accordance with IRB operating procedures.

Signature of Principal Investigator: _____Date_____
(Signature)

Approval of
Department or Section Chair: _____Date_____
(Signature)

APPENDIX B: Application for HIPAA Waiver

Application for HIPAA Waiver

Gundersen Health System
Scientific Research/
Human Subjects Committee

IRB #: _____

Date Approved: _____

For Office Use Only

A **Completed, Printed** response to the following is required for review of your application:

Date Submitted:

Principal Investigator: Telephone:
Email:

Co-Investigators:

Coordinator: Telephone:

Study Title:

Cooperative or Company number (if appropriate):

Source of Funding:

Expected Number of subjects: Local: National:

Duration of Data Gathering: From: To:

Expected Date of Completion of Project:

1. In your estimation, how significant for the advancement of knowledge is this research?

   ☐ Outstanding ☐ Significant ☐ Greater than Average ☐ Interesting

2. Will any of the investigators receive any direct compensation from sources other than Gundersen Health System for conducting this study? ☐ Yes ☐ No
   --If your answer is yes, please explain:

3. Do you have any financial, consulting, or other arrangement with the company sponsoring the research? ☐ Yes ☐ No
   --If your answer is yes, please explain:

4. Do you have or claim any intellectual property rights in the drugs or medical devices that are the subject matter in the study? ☐ Yes ☐ No
   --If your answer is yes, please explain:

5. Do you have any financial relationships noted on your Gundersen Health System Conflict of Interest Disclosure Statement related to this research protocol? ☐ Yes ☐ No
   --If your answer is yes, please attach a copy of the disclosure statement.

6. In addition to the completion of this questionnaire, you must also submit:
   A. a brief abstract describing the study;
   B. a copy of the complete protocol that includes:
      (1) hypothesis to be tested
      (2) background information
      (3) study design. In the study design you must answer the following questions:
         a. How will patient identifiers be protected from improper use and disclosure?
         b. Is there a plan to destroy patient identifiers?
         c. Are there assurances that information will not be reused or disclosed?
         d. Is there another way to obtain this information?
         e. Could the research be done without use of patient identifiers?
         f. How much of the patient's chart will you need to look at to abstract the data?
         g. How many charts will be reviewed?
      (4) methods to be used for analysis
      (5) itemized and total budget
      (6) bibliography

I request IRB review of this study and, if approved, I accept responsibility for conducting the study in accordance with IRB operating procedures.

Signature of Principal Investigator: _____ Date_____

APPENDIX C: Research Committee Reviewer Checklist

Gundersen Health System Research Committee
Reviewer Checklist

Date of RC Review:

Scheduled Date of HSC/IRB Review:

IRB #:

RC Reviewer:

Circle response: Y=Yes N=No TBD=To Be Discussed

1. Is the study adequately designed?	Y	N	TBD
2. Are risks acceptable and have they been minimized?	Y	N	TBD
3. Does the study have a clear benefit?	Y	N	TBD
4. Is there adequate protection of human subjects?	Y	N	TBD
5. Is there a reasonable budget for this study?	Y	N	TBD
6. Is there a funding source for this study?	Y	N	TBD
7. Is the IRB questionnaire filled out completely?	Y	N	TBD
8. Does the proposed study require a laboratory consultant?	Y	N	TBD

APPENDIX D: HSC/IRB Reviewer Checklist

Gundersen HSC/IRB
Reviewer Checklist

Date of HSC/IRB Review:

Date of RC Approval:

IRB #:

Study Title:

Reviewer:

Response key: Y=Yes N=No TBD=To Be Discussed

1. Are risks acceptable and have they been minimized?	Y	N	TBD
2. Does the study have a clear benefit?	Y	N	TBD
3. Is consent form complete?	Y	N	TBD
Should an assent form be added?	Y	N	TBD
Are corrections needed?	Y	N	TBD
Are there concerns about the consent process?	Y	N	TBD
4. Is the selection of subjects equitable/fair?	Y	N	TBD
5. Are privacy and confidentiality protected?	Y	N	TBD
6. Will participation be voluntary?	Y	N	TBD
7. Is a potential financial conflict of interest involved?	Y	N	TBD

APPENDIX E: HIPAA Checklist

HIPAA Checklist

Scheduled Date of HSC/IRB Review:

IRB #:

Title:

Response key: Y=Yes N=No

1. Does the information involve only decedents?	Y	N
2. Is the information being reviewed in preparation for research?	Y	N
3. Does the disclosure of protected health information involve more than minimal risk to individuals?	Y	N
4. Is there an adequate plan to protect the identifiers from improper use and disclosure? Explain:	Y	N
5. Is there an adequate plan to destroy the identifiers at the earliest opportunity? Explain:	Y	N
6. Are there adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity except as required by law?	Y	N
7. Will a waiver adversely affect the privacy rights and welfare of the individual?	Y	N
8. Can the research be conducted without a waiver?	Y	N
9. Is the risk to privacy reasonable relative to the expected benefit?	Y	N

10. Could the research be practicably conducted without access to the use of protected healthcare information? Y N

11. How many charts or records will be reviewed?

12. Is the minimum necessary information being released? Y N

APPENDIX F: Consent Form Template and Sample Consent Form

It is required that the consent forms exclusively use pronouns either in the first person (I, my) or second person (you, your) to refer to research participants. Consent forms that mix first and second person pronouns to refer to research participants will not be accepted.

For more information about the wording and content of the consent form, please consult the *Researcher's Guide to Project Review at Gundersen Health System* and the *Consent Form Template.*

SAMPLE CONSENT FORM

The following sections/topics need to be included in the consent form:

- Background (the reason the study is being conducted)
- Purpose of the Study (one sentence only, which is consistent with the purpose described in the protocol)
- Description of Procedures
- Risks and Discomforts
- Benefits
- Financial Responsibility
- Contact Persons (include telephone number for the investigator and Chair of the HSC)
- Voluntary Participation
- Confidentiality (Must comply with HIPAA regulations for authorization to release records)

The following language is required:

I have read all the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this study. Upon signing this form, I will receive a copy.

_____ _____

(Participant Signature) (Date)

I affirm that _____ has read and signed this consent form in my presence today and that there were no questions that had not been answered by the investigator. This person understood and willingly gave consent to participate in this study.

_____ _____

(Signature of Researcher obtaining consent) (Date)

_____has read and signed this consent form and told us there are no questions that have not been answered by the researcher. The participant says the consent

form is understood and the consent is willingly given. We are writing our names below as witnesses and we believe the participant understands what is being done and has willingly signed the consent form. (Note: one or two witnesses are determined by the HSC)

_____

(Witness Signature) (Date)

_____

(Witness Signature) (Date)

The IRB may approve a consent procedure that does not include or which alters some or all of the elements of informed consent set forth above, or may waive the requirements to obtain written informed consent if the IRB finds that:

1. the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context;

2. the waiver or alteration will not adversely affect the rights and welfare of the participant;

3. the research could not practically be carried out without the waiver or alteration;

4. whenever appropriate, the participants will be provided with additional pertinent information after participation; and/or

5. the only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant's wishes will govern.

In cases in which documentation is waived, the IRB may nevertheless require an investigator to provide each participant with a written statement regarding the research.

Informed Consent for Minors

PERMISSION

I/We have read this research study and/or have talked it over with the physician/nurse practitioner/study nurse to my/our satisfaction. I/We knew enough about the research study to judge that I/we want my/our child to take part in it.

I/We understand that my/our child has not given up any rights by agreeing to participate in this study.

I/We hereby give my/our permission to have my/our child participate in this research study.

Dated

SIGNATURES:

_____

_____

Print Name(s) of Parent(s) or legal guardian:

_____

_____

ASSENT

I have read this research study and/or have talked it over with the physician/nurse practitioner/study nurse to my satisfaction. I know enough about the research study to judge that I want to take part in it.

I understand that I have not given up any rights by agreeing to participate in this study.

I hereby assent to participate in this research study.

Dated

CHILD'S SIGNATURE:

_____

Print Name of Child:

_____

The above form must be modified to use the correct pronouns and should have the assent statement and require the child's signature except in those studies in which the children are all not capable of assent.

Adequate provisions are to be "made for soliciting the assent of children, when in the judgment of the HSC, the children are capable of providing assent." 45 CFR 46.408. All children 14 or older must give assent to participate in research. The HSC will determine if assent is required for particular proposals for children between 7 and 13. Assent is not needed for children younger than 7.

1. WHEN ONE PARENT'S PERMISSION IS ENOUGH

   A. The permission of one parent is sufficient for research where there is no greater than minimal risk to the children; or

   B. There is

      "more than minimal risk to children ... presented by an intervention or procedure that holds out the prospect of direct benefit for the individual [patient] or by a monitoring procedure that is likely to contribute to the [patient's] well being only if the IRB finds that:

      "(1) The risk is justified by the anticipated benefit to the [patient];

      "(2) the relation of the anticipated benefit to the risk is at least as favorable to the [patient] as that presented by available alternative approaches; and

      "(3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians."

   See 45 CFR 46.404, 46.405 and 46.408.

2. WHEN BOTH PARENTS' PERMISSION IS REQUIRED

   A. The permission of both parents is required, unless one parent is deceased or one parent alone has legal responsibility for the care and custody of the child, when research involves

      "greater than minimal risk and no prospect of direct benefit to individual [patients] is foreseen but is likely to yield generalized knowledge about the [patient's] disorder or condition."

   The IRB should approve such research "only if the IRB finds that:

"(1) the risk represents a minor increase over minimal risk;

"(2) the intervention or procedure presents experiences to [patients] that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

"(3) the intervention or procedure is likely to yield generalizable knowledge about the [patients]disorder or condition which is of vital importance for the understanding or amelioration of the [patient's] disorder or condition; and

"(4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in Section 46/408." See 45 CFR 46.406.

B. The permission of both parents is also required for research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children is done under the conditions of 45 CFR 46.407. The Secretary of the Department of Health and Human Services must make the findings required in 45 CFR 46.407 before this research is approved.

APPENDIX G: Guidelines for Preparing a Prospective Research Study Protocol

Gundersen Health System Guide to Writing a Prospective Research Protocol

Application for approval of a prospective research project at Gundersen Health System requires:

- **2 copies of a complete protocol** prepared according to the following guidelines
- a completed **IRB Questionnaire**

The following guidelines are for protocols for prospective research studies. Protocols for compassionate use are handled differently. Refer to PROCEDURE FOR SINGLE USE OF A TEST ARTICLE *on pages 21-22* of the Institutional Review Board Guidelines for Research on Human Participants *located under "Forms and Information for Researchers" on the Research page of the Gundersen Health System Website. If it is anticipated that more than 2 patients will be entered on a single patient/ compassionate use protocol, the protocol will ordinarily be treated as a scientific protocol.*

For investigators requesting IRB approval for a protocol developed elsewhere, for example, a master's student thesis proposal or a multi-institutional proposal, the original copy of the proposal may be submitted if the proposal clearly addresses all of the issues listed below. You must submit **2 copies of a complete protocol** and a **completed IRB Questionnaire** to the Director of the Research Committee in order to begin the research approval process. All research conducted at Gundersen Health System requires Research Committee and/or Institutional Review Board (IRB) approval. A complete protocol will contain:

1. Title

The title should briefly and concisely describe the project's *central objectives* and *population being investigated*. For example, the title "Detection of Left Atrial Appendage Thrombus in Patients Referred for Cardioversion with Unknown or Naive Coagulation Status: Comparative Analysis of Cardiac Magnetic Resonance Imaging and Transesophageal Echocardiogram" describes for the reader the central objective (to compare two techniques for detecting left atrial appendage thrombus) and the study population (patients referred for cardioversion with unknown or naïve coagulation status).

2. Project Summary (Abstract)

The summary should

A. express in a clear concise fashion the hypothesis to be tested or research question to be answered;
B. briefly describe the study design and methodology (experimental, qualitative, survey);
C. contain a statement of the study's objective(s) (new area of investigation, validation of a therapy, change in practice); and
D. define participant selection (department/unit involved, population to be selected, sample size).

3. Background Information

In this section of your protocol, it should be clear that you have thoroughly reviewed the relevant literature and have developed your hypothesis or research question within that

context. It is also in this section that you will make a convincing argument that your proposed study will make a valuable contribution to knowledge. Why is your research needed? That is, what will your study contribute to the existing body of knowledge? Will it fill a gap in knowledge? Does it challenge established knowledge? Or does it attempt to resolve an existing controversy? And finally, what is the magnitude of the problem? What is the benefit of knowing—or the cost of not knowing—the new knowledge your study will generate, in terms of how many people might be helped, how much money might be saved, etc.

What are your research goals and objectives, general and specific?

4. Study Design

Be specific about how you plan to gather the data necessary to test your hypothesis or answer your research question. Describe your study population, eg, how many people will you study, and what are your inclusion and exclusion criteria? What types of variables will you use, and how will you measure them? Will you use surveys? Chart reviews? Interviews? Will informed consent be required? Who will obtain it, and in what setting? Will participants receive remuneration of any kind? If so, indicate amount, when they will receive it, and why you believe remuneration is required.

Discuss the potential difficulties and limitations of the proposed approach to achieve the goals.

List any drugs, treatments, vaccines, or interventions of any kind that will be employed and whether they are registered, unregistered, new, or presently in use in the United States. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be taken.

Identify the likely place/location of personnel, supply storage, and data storage. How will patient identifiers be protected from improper use and disclosure? Is there a plan to destroy patient identifiers? Are there assurances that information will not be reused or disclosed?

Include drafts of proposed registration forms, consent forms, questionnaires, surveys, tools for recording data collection, etc. in an Appendix, indicating their state of preparation.

5. Methods to Be Used for Analysis

Indicate how you will analyze the data you collect, whether quantitative or qualitative. What statistical, non-statistical, or analytical techniques will you use to evaluate the data? Identify any software packages that you plan to use.

6. Budget

Itemize all expenses into personnel, supplies, equipment, and miscellaneous. Include percent of effort to be committed to the project for all individuals involved, even if no dollars are budgeted. Give sufficient detail on each item to determine how you arrived at the requested figure.

7. Informed Consent

Provide a copy of the informed consent form that participants will be asked to sign (if needed). See section on Guidelines for Informed Consent and APPENDIX F in the *Institutional Review Board Guidelines for Research on Human Participants* located under "Forms and Information for Researchers" on the Research page of the Gundersen Lutheran Website.

8. Bibliography

Provide a bibliography that includes all pertinent publications.

9. Appendix

Include copies or descriptions of any questionnaires, interview guides, registration forms, data collection sheets, etc., indicating their state of preparation.

APPENDIX H: IRB Progress/Final Report Form

APPENDIX H: IRB Progress/Final Report Form

IRB #

Principal Investigator

GUNDERSEN IRB PROGRESS/FINAL REPORT FORM

Protocol Title:

Date of IRB Approval:

Institutional policy requires periodic review of and a final report for all human research protocols approved by the IRB. This report must be received by **.**
If the report is not received by this day, collection of data for this study must stop. You must also include a copy of the current informed consent form. If you have any questions, please contact the Chair of the IRB. *Please return this form to Melinda - IRB Coordinator - Mail Stop C03-006B.*

		YES	NO
1.	Is this protocol still an active study? (If no, please answer questions 5 & 6 below and document your final report on the back of this form.)	☐	☐
2.	Are participants currently under therapy and/or are new participants still being entered or recruited for this study? How many participants have been entered to date?_____ How many participants are actively under protocol?_____	☐	☐
3.	Prior to approval of your protocol, you submitted an IRB questionnaire. Would the answers now to the questions in the questionnaire be identical to the answers you originally gave? (If no, please explain on back.)	☐	☐
4.	Has your financial relationship with the sponsor of this study changed in any way in the past year? (If yes, please document on back.)	☐	☐
5.	Have any unanticipated problems or untoward side effects occurred in the study? (Please consider safety reports for the past year [summary attached/not attached] and consider if the consent form needs to be amended.) (If yes, please explain on back.)	☐	☐
6.	Have you made any changes to the consent form not previously approved? (If yes, please send a copy of the consent form you are using/used with the changes highlighted.)	☐	☐
7.	Should there be any changes in the consent form or consent process? (If yes, please explain on back.)	☐	☐

8. Have you made any changes in research personnel? (If yes, please explain on back.) ☐ ☐

9. Please provide any <u>new</u> (since submission) literature, interim reports, or data that have a bearing on the risk of conducting this study.

Signature of Principal Investigator: _____
Date:_____

PROGRESS REPORT COMMENTS: (NOTE: Use additional sheets if necessary. Please specify the number of the question you are commenting on.)

FINAL REPORT COMMENTS:

Date protocol was stopped (date when all data has been collected at our site):

Reason stopped:

Number of subjects planned:_____
Number of subjects enrolled:_____
Number of subjects completed:_____
Number of subjects who experienced or are experiencing adverse effects:_____
(Describe any trends noted in adverse effects)

Close-out procedures are scheduled to be completed by a representative of the sponsor on (date):_____

Findings (attach additional sheets if necessary):

APPENDIX I: Progress/Final Report for Approved HIPAA Waivers

APPENDIX I: Progress/Final Report for Approved HIPAA Waivers

Principal Investigator **IRB #**

GUNDERSEN IRB PROGRESS/FINAL REPORT FORM FOR APPROVED HIPAA WAIVERS

Protocol Title:

Date of IRB Approval:

Institutional policy requires periodic review of and a final report for all human research protocols approved by the IRB. This report must be received by **.**
If the report is not received by this day, collection of data for this study must stop.
If you have any questions, please contact the Chair of the IRB. *Please return this form to Melinda - IRB Coordinator – Mail Stop C03-005.*

		YES	NO
1.	Is this study complete? (If yes, please answer questions #3 and #4below) (If no, please answer questions #2 and #3 below)	☐	☐
2.	Have there been any changes to the original proposal, methods, staff, etc? (If yes, please explain):	☐	☐
3.	Has there been any unplanned or unintended release of PHI? (If yes, please explain):	☐	☐
4.	Has all data and/or PHI been destroyed or returned as described in original proposal?	☐	☐

Signature of Principal Investigator: _____ Date: _____

APPENDIX J: Non-employee Researchers

Guidelines for Approval of Non-employee Researchers at
Gundersen Clinic, Ltd. and
Gundersen Lutheran Medical Center, Inc.

In order to promote the research activities at Gundersen Health System and improve patient care, at times it will be desirable to involve or to collaborate with non-employee researchers. These Guidelines are developed to determine how and when this use of non-employee researchers may be approved.

CRITERIA FOR APPROVAL

1. Professionals who are not employees who desire to do research at Gundersen Health System.

   When requests are made by health professionals or other researchers who do not work at Gundersen Health System to conduct a research project using patients or patients' records, the following criteria will be used to provide them with the status of Adjunct Research Staff.

   A. The professionals must be determined to have the appropriate training, experience, and resources to conduct the study.
   B. The proposed study must have merit, be considered well designed, meet all IRB requirements, including the required ethics education, and fit into the mission of Gundersen Health System.
   C. Confidentiality of data and use of space and other resources has been reviewed and addressed to the satisfaction of the HSC/IRB and Research Committee.
   D. There must be a clear collaborative relationship with an employee of Gundersen Health System as determined by a letter of support from that employee. That employee must agree to oversee the protection of patient privacy and confidentiality.
   E. Any Departments impacted or involved by the proposed study must be notified, and the study must receive the written support of the Department head.
   F. The non-employee researcher must sign a confidentiality agreement, and will be limited in access to only the patient's charts and the determined content needed for the study. Thus the privilege of access to the data will be only to the patients' charts needed to determine content and only to the data in the charts needed.
   G. The non-employee must work through volunteer services and meet the requirements of that department.

2. Use of volunteers for data collection/research assistants.

   At times Gundersen Health System researchers may want to use volunteers to collect data for a research project. The use of volunteers will be considered when:

   A. there is no other way the data can be collected;
   B. the study is considered of merit and advances the mission of Gundersen Health System;
   C. the Department head has been informed and has provided written approval;
   D. the volunteer is considered to have the appropriate education and judgment required for the task;

E. the researcher will be able to provide adequate supervision and oversight of the data collection and the protection of patient privacy and confidentiality; and
F. adequate protections exist to protect patient confidentiality.

The volunteer must sign a confidentiality agreement and complete training as needed. The volunteer must also work through volunteer services and meet the requirements of that department. The use of a family member to collect data as a volunteer is strongly discouraged because the familial relationship makes oversight more difficult.

APPROVAL PROCESS

Approval of non-employee researchers and volunteer research assistants will be the responsibility of the Research Committee and the HSC/IRB. Both Committees must approve of the appointment before the person can partake or start any data collection. Another person or Committee cannot reverse a disapproval of either Committee. Disapproval can be addressed by submitting new information to the Committee that gave the disapproval.

If one of the Committees does not approve of the use of the non-employee for the proposed research project, the Committee will put into writing the reasons for its decision and provide the vote tally for the decision.

APPENDIX K: Sample Data Use Agreement

DATA USE AGREEMENT BETWEEN GUNDERSEN HEALTH SYSTEM AND ADJUNCT RESEARCH ASSOCIATE

FOR VALID CONSIDERATION, Gundersen Clinic, Ltd. and Gundersen Lutheran Medical Center, Inc. (collectively "Gundersen Health System") agree to provide the undersigned Adjunct Research Associate with access to Gundersen Health System's patient healthcare records including, without limitation, Gundersen Health System's electronic medical records and Clinical Work Station, for purposes of conducting research. This authorization is subject to the following terms and conditions:

ADJUNCT RESEARCH ASSOCIATE:

Printed Name:

Home Address: City, State, Zip Code:

Home Telephone:

RESEARCH PROJECT:

PRINCIPAL INVESTIGATOR: Printed Name:

DURATION OF RESEARCH: (circle one) year(s) month(s),

commencing on , 201

and ending not later than , 201 .

ADDITIONAL TERMS: The Adjunct Research Associate shall comply with all of the terms and conditions in Exhibit A.

IN WITNESS WHEREOF, the parties have entered into this Agreement, including the terms in Exhibit A, effective January 1, 2006.

GUNDERSEN CLINIC, LTD. and GUNDERSEN LUTHERAN MEDICAL CENTER, INC.

ADJUNCT RESEARCH ASSOCIATE

By:_____

Name: _____

Title: _____

EXHIBIT A

STANDARD TERMS AND CONDITIONS

1. **PURPOSE.** The purpose of this Agreement is set forth the terms and conditions governing the Adjunct Research Associate's (a) affiliation with Gundersen Health System for purposes of conducting the Research Project, and (b) access to and use of Gundersen Health System's patient health information including, without limitation, electronic medical records and Clinical Work Station.

2. **DURATION; TERMINATION.** The duration of this Agreement is set forth on the cover page. This Agreement and the Adjunct Research Associate's access to Gundersen Health System's patient healthcare records including, without limitation, electronic medical records and the Clinical Work Station: (a) may be terminated by Gundersen Health System for cause at any time, with or without prior notice; and (b) shall terminate automatically upon termination of the Adjunct Research Associate's involvement in the Research Project.

3. **ACCESS TO PATIENT HEALTHCARE RECORDS.** Gundersen Health System agrees to provide the Adjunct Research Associate with access to Gundersen Health System's patient healthcare records including, without limitation, electronic medical records and Clinical Work Station, for the limited purpose of conducting the Research Project. The Adjunct Research Associate shall:

   A. not access patient health information for any patient other than those whose patient health information is being studied in connection with the Research Project;

   B. use patient health information only for the Research Project for which such patient health information is being provided to the Adjunct Research Associate;

   C. not release patient health information to any person or entity not connected with or involved in the Research Project; and

   D. ensure that the final report, study or product relating to the Research Project does not reveal any demographic or other information that may serve to identify the patient whose patient health information is being released.

4. **DESTRUCTION OF COPIES.** If patient health information is photocopied or printed during the Research Project, the Adjunct Research Associate shall ensure that:

   A. such documents are not removed from the premises of Gundersen Health System; and

   B. such documents are disposed of by depositing them in designated confidential containers or, if no confidential container is available, by shredding them or tearing them into quarters, as required by Gundersen Health System Policy No. HR-205.

5. **COMPLIANCE.** The Adjunct Research Associate shall comply with all applicable federal and state laws, Joint Commission for the Accreditation of Healthcare Organization standards, and Gundersen Health System policies relating to the confidentiality of patient health information.

6. **AMENDMENTS.** This Agreement may not be amended except pursuant to a written document signed by both Parties.

7. **ASSIGNMENT.** This Agreement may not be assigned by the Adjunct Research Associate to any other person or entity without the prior written consent of Gundersen Health System.

8. **AUDITS; ACCESS TO BOOKS AND RECORDS; HIPAA COMPLIANCE.**

   A. To the extent that section 952 of the Omnibus Budget Reconciliation Act of 1980 and applicable regulations are applicable to this Agreement, the Adjunct Research Associate shall, until four years after the expiration of this Agreement, comply with all requests by the Comptroller General of the United States, the Secretary of the Department of Health and Human Services, and their duly authorized representatives for access to this Agreement and to all books, documents and records necessary to verify the Adjunct Research Associate's access to Gundersen Health System's patient health information hereunder and the purpose of such access. In any event, the Adjunct Research Associate shall immediately notify Gundersen Health System upon receipt by the Adjunct Research Associate of any such request for the Agreement and any other books, documents and records relating thereto, and shall provide Gundersen Health System with copies of any such materials.

   B. If and to the extent, and so long as, required by law and not otherwise, the Adjunct Research Associate does hereby assure Gundersen Health System that the Adjunct Research Associate shall appropriately safeguard protected health information made available to or obtained by the Adjunct Research Associate from Gundersen Health System. The Adjunct Research Associate agrees to comply with applicable requirements of law relating to protected health information to the extent Gundersen Health System would be required to comply with such requirements. The commitment by the Adjunct Research Associate set forth in this Agreement constitutes a contract establishing the permitted and required uses and disclosures of such protected health information by the Adjunct Research Associate.

   C. The Adjunct Research Associate shall: (i) not use or further disclose such patient health information other than as permitted or required by this Agreement; (ii) not use or further disclose such patient health information in a manner that would violate the requirements of applicable law, if done by Gundersen Health System; (iii) use appropriate safeguards to prevent use or disclosure of such patient health information other than as provided for by this Agreement; (iv) report to Gundersen Health System any use or disclosure of such patient health information not provided for by this Agreement of which the Adjunct Research Associate becomes aware; (v) ensure that any other persons or entities to whom the Adjunct Research Associate provides patient health information received

from Gundersen Health System agree to and comply with the same restrictions and conditions that apply to Gundersen Health System with respect to such information; (vi) make available patient health information in accordance applicable law; (vii) make the Adjunct Research Associate's practices, books, and records, if any, relating to the use and disclosure of patient health information received from Gundersen Health System available to the Secretary of the Department of Health and Human Services for purposes of determining the Adjunct Research Associate's compliance with applicable law; and (viii) upon expiration or earlier termination of the Agreement, return or destroy all patient health information received from Gundersen Health System that the Adjunct Research Associate still maintains in any form and retain no copies of such information; and (ix) incorporate any amendments or corrections to patient health information when notified pursuant to applicable law.

9. **SEVERABILITY.** If any provisions in this Agreement are determined to be void and unenforceable for any reason, the remaining provisions shall remain in full force and effect to govern the conduct and relationship of Gundersen Health System and the Adjunct Research Associate.

10. **ENTIRE AGREEMENT.** This Agreement constitutes the entire understanding and agreement between Gundersen Health System and the Adjunct Research Associate relating to their relationship, and supersedes all prior understandings, representations and agreements relating thereto. This Agreement may not be amended except pursuant to a written agreement signed by both Gundersen Health System and the Adjunct Research Associate.

11. **GOVERNING LAW; SEVERABILITY.** The validity, construction and interpretation of this Agreement, and the rights and duties of the parties hereunder shall be governed by the laws of the State of Wisconsin without regard to conflicts of law principles. If any provision of this Agreement is determined to be unenforceable or invalid for any reason, the remainder of this Agreement shall remain in full force and effect to govern the parties' conduct and relationship.

APPENDIX L: Protocol Violations and Deviations

Definition of and Procedure for Protocol Violations and Deviations

Definitions
A violation or deviation is any instance in which the current IRB-approved protocol is not followed. For the purpose of this policy, *protocol* includes the protocol itself, IRB Questionnaire, consent form, recruitment materials, or any materials reviewed and approved by the IRB.

Violations
- increase risk in the area of participant safety, rights, welfare; or
- significantly affect the integrity of research data; or
- violate Inclusion/Exclusion criteria; or
- render the informed consent document inaccurate.

Deviations
- do not increase risk in the area of participant safety, rights, welfare; or
- do not significantly affect the integrity of research data; or
- do not violate Inclusion/Exclusion criteria; or
- do not render the informed consent document inaccurate.

Reporting Procedure for Violations and Deviations:
- All protocol **violations** are to be reported in writing to the Human Subjects Committee/IRB in a timely manner.
- Protocol **deviations** are not required to be submitted to the Human Subjects Committee/IRB; however, they will be granted expedited IRB review if requested.