The Nebraska Methodist Hospital Institutional Review Board

The Official Institution Review Board for
the Following Affiliates of the Nebraska Methodist Health System, Inc.:

Nebraska Methodist Hospital and Methodist Women's Hospital
Jennie Edmundson Memorial Hospital d/b/a Methodist Jennie Edmundson
Methodist Fremont Health and Fremont Health Clinic
Physicians Clinic, Inc., d/b/a Methodist Physicians Clinic

Handbook

Guidelines for the
Protection of Human Research Subjects

(Approved by the IRB on January 24, 2022)

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Federalwide Assurance FWA00003377

Nebraska Methodist Hospital and Methodist Women's Hospital FWA00003377
Jennie Edmundson Memorial Hospital d/b/a Methodist Jennie Edmundson FWA00006650
Methodist Fremont Health FWA00031850
Physicians Clinic, Inc., d/b/a Methodist Physicians Clinic FWA00027207

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TABLE OF CONTENTS

I. INTRODUCTION

A. BACKGROUND

Medical research involving humans as research subjects ("Subject(s)") is widely accepted as an appropriate and critical activity in the development of new drugs, devices and methods for the prevention, treatment and eventual cure of human diseases. Thousands of research studies are conducted in the United States, sponsored by cooperative research groups, research institutions, pharmaceutical companies, device manufacturers, physicians, and other researchers. The U.S. Food and Drug Administration ("FDA") requires extensive research studies as a pre-condition to the marketing of most new drugs and devices, and the U.S. Department of Health and Human Services ("HHS" or "DHHS") actively supports and regulates numerous research projects.

Research involving Subjects must be consistent with fundamental ethical principles, including the absolute requirement that Subjects participate only after truly informed, voluntary consent, the requirements that the research follow scientifically valid protocols, the risks to Subjects are proportionate to the anticipated benefits to the Subject and/or to society at large, and that financial and other conflicts of interest are properly monitored and avoided to the maximum extent possible. The Investigators, Sponsors, HHS and FDA all have substantial responsibilities in assuring compliance with ethical and legal standards. The Institutional Review Board or "IRB" exists for the purpose of protecting Subjects through the approval, disapproval, and monitoring of research studies in light of ethical standards.

B. PURPOSE AND ROLE OF IRB

The Nebraska Methodist Hospital ("NMH") Institutional Review Board (the "IRB") is organized and operates under the authority of the President of The Nebraska Methodist Hospital. The IRB's role is to review proposed studies (referred to herein as "study(ies)" or "research") or other research related matters that impact patients of any affiliate of the Nebraska Methodist Health System, Inc. ("NMHS"). Affiliates of NMHS ("Affiliates") include:

- Nebraska Methodist Hospital
- Methodist Women's Hospital
- Physicians Clinic, Inc., d/b/a Methodist Physicians Clinic
- Methodist Jennie Edmundson
- Methodist Fremont Health
- Fremont Health Clinics

Broadly, the IRB ensures:

- Risks to Subjects are minimized;
- Risks to Subjects are reasonable in relation to anticipated benefits;
- Selection of Subjects is equitable;
- The privacy of Subjects is maintained and protected;
- Protections are in place for Subjects who are likely vulnerable to coercion and undue influence due to physical or mental illness, economic or educational disadvantage, or other factors;
- Proper informed consent is to be obtained; and
- Other appropriate safeguards are maintained as necessary to assure the safety of Subjects.

The IRB has authority over research at all Affiliates through a process called 'federalwide assurance' ("FWA").

Under the Common Rule and FDA Regulations, each institution engaged in research that is conducted or supported by a federal department shall provide written assurance, called a Federalwide Assurance, that it will comply with the Common Rule and FDA Regulations, as applicable. Each Affiliate that engages in research shall have an active FWA on file with the DHHS Office for Human Research Protections. An FWA shall be signed by the President of each Affiliate. An FWA consists of the following statements:

- The institution will be guided by a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research, such as the Declaration of Helsinki or Belmont Report.

- The institution will conduct all human subject research under the terms of the FWA.

- The institution will conduct research activities in compliance with applicable laws, regulations, policies and guidelines.

- The institution has written procedures for ensuring prompt reporting to the IRB, institutional officials, or the government as described in this Handbook.

- The IRB has sufficient meeting space and support to carry out its duties

- The institution will rely on an IRB for review of research, and specify which IRB the institution will rely on.

- The institution will review and update its FWA every five (5) years.

The IRB at NMH is the only internal IRB within NMHS authorized to oversee human subject research at other Affiliates of NMHS. As such, all Affiliates engaged in research have indicated in their FWA that they rely on the IRB for review of research matters that take place or affect NMHS. This is how the IRB has authority over research at all Affiliates.

II. NMH IRB STATEMENT OF ETHICAL PRINCIPLES AND POLICY

A. ETHICAL PRINCIPLES

NMHS and the IRB are guided by the ethical principles for all research involving humans as Subjects as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report"), a copy of which is attached as Exhibit A. In addition, the requirements set forth in 45, C.F.R. Part 46 of the Code of Federal Regulations (the "Common Rule") will be met for all applicable HHS-regulated research, and the requirements set forth in the regulations of the Food and Drug Administration (21 CFR Parts 50 and 56, referred to herein as the "FDA Regulations") will be met as applicable to studies of investigational drugs and devices. Other applicable regulations include 21 C.F.R. Part 54 (Financial Disclosure by Clinical Investigators), 21 C.F.R. Parts 312 (Investigational New Drug Application), 21 C.F.R. Part 314 (Applications for FDA Approval to Market a New Drug), 21 C.F.R. Part 812 (Investigational Device Exemptions), and 21 C.F.R. Part 814 (Premarket Approval of Medical Devices).

B. INSTITUTIONAL POLICY

1. Appropriate measures will be taken to protect the rights and welfare of Subjects. Before Subjects are involved in research, proper consideration shall be given to, without limitation, the following:

    a. The risks and burdens to the Subjects;

    b. The anticipated benefits to the Subjects and others;

    c. The importance of the knowledge that may reasonably be expected to result;

    d. The informed consent procedures and documents to be employed;

    e. The confidentiality of Subjects; and

    f. The existence or non-existence of possible conflicts of interest or financial incentives adversely affecting the research process.

2. NMHS, through the IRB, will be responsible for the review of all research involving Subjects within the scope of the IRB's authority, including continuing review of research.

3. NMHS and all persons involved in human subject research will comply with federal, state, and local laws and regulations governing such research.

4. NMHS encourages and promotes constructive communication among the research administrators, department heads, Investigators, clinical care staff, Subjects, institutional officials and others involved in research as a means of maintaining a high level of awareness regarding the safeguarding of the rights and welfare of Subjects.

5. NMHS, acting through the IRB, will exercise appropriate administrative overview throughout each year to ensure its practices and procedures designed for the protection of the rights and welfare of Subjects are being effectively applied.

6. The IRB will consider additional safeguards in research when research involves prisoners, pregnant women, minors, individuals who are mentally disabled, other potentially vulnerable groups (taking into account the social determinants of health) and human in vitro fertilization.

7. NMHS shall make available to each individual at the institution conducting or reviewing human subject research (e.g., research investigators, department heads, research administrators, research reviewers) a copy of this Manual and the Belmont Report.

8. NMHS and the IRB will encourage and support continuing education for IRB members and Investigators.

III. OVERVIEW OF CLINICAL RESEARCH AT NMH

A. INTERESTED PARTIES. In addition to the IRB and the President, and in addition to the study Subject, the following individuals and entities are involved in the IRB/clinical research process:

1. IRB Members, Scope of Authority. The initial members of the IRB were selected and appointed by the President of NMH. Subsequent members of the IRB have been and are to be selected by Approval (defined below) of the IRB. The IRB has authority to review, approve/disapprove, and monitor on an ongoing basis, all research involving human subjects that is conducted in whole or in part by, through, or at any Affiliate of NMHS. Approval is effective once an IRB-approved letter is issued by the IRB Office and continues unless and until the approval is revoked or modified by the IRB. Disapproval of a study by the IRB is effective once an IRB-approved letter is issued by the IRB Office.

2. FDA and HHS. Generally, the FDA creates and enforces federal laws governing drugs and devices, including the FDA Regulations. New drugs and devices can be marketed only with the FDA's approval. Prior to approval, drugs and devices go through several stages of FDA-supervised research and investigation. Under the FDA Regulations, there must be an Institutional Review Board that pre-approves, and supervises, the investigation conducted by local investigators. Similarly, HHS creates and enforces federal laws governing most other types of human subject research in a hospitals and clinics. The Common Rule requires that an Institutional Review Board pre-approve and supervise research conducted by the local physician-investigators.

3. Investigators. The Investigator is the physician or other qualified personnel responsible for the conduct of a study at NMHS or any one of its Affiliates. In Sponsored (defined below) studies, the Investigator has established an agreement and working relationship with the Sponsor or a Sponsor's contractor before seeking IRB approval. Investigators are typically either (a) members of an Affiliate of NMHS's Medical Staff (defined below), (b) employees of NMHS or any Affiliate, or (c) separately authorized to render services at an Affiliate of NMHS and are subject to separate credentialing. If more than one Investigator is conducting the same study, a principal investigator ("Principal Investigator") will be determined by the parties involved, and such Principal Investigator oversees the other Investigators, referred to as "Secondary Investigators." Principal Investigator and Secondary Investigators may generally be referred to as "Investigator(s)."The Principal Investigator may delegate authority to a Secondary Investigator so long as such delegation complies with the terms of the applicable Protocol and the Sponsor in acceptable to such delegation.

4. Sponsor. Studies are typically "Sponsored" by an external entity. When an organization, the government or a company sponsors a study (a "Sponsor"), it could mean they created the study, pay for the study, have oversight over the study, have access to results, or all of the above. Sponsors may also be local groups or in some cases, the Investigator. The Sponsor has primary responsibility for obtaining any required approval of the study from the FDA and/or HHS, and for reporting to the FDA and/or HHS as applicable. However, the Investigator and the IRB may also be subject to these requirements.

5. Medical Staff. The "Medical Staff" of each Affiliate is a body of health care providers granted privileges to perform patient care services at such Affiliate, appointed through

written procedures of each Affiliate. Each Affiliate has their own procedures for appointment of health care providers to the Medical Staff. For each study, there must be an Investigator who is on the Medical Staff or an employee of the applicable Affiliate. Investigators who are on the Medical Staff of an Affiliate operate under the authority of both the IRB and the Medical Staff.

6. IRB Manager. The "IRB Manager" is the individual employed by NMH who is charged with providing administrative support to the IRB.

7. Contract Research Organization/Study Management Organization. A Contract Research Organization (CRO) or Study Management Organization (SMO) coordinates or manages studies on behalf of a Sponsor. CROs/SMOs, if utilized by a Sponsor, have a separate agreement with such Sponsors to conduct certain research-related functions. Varying levels of authority are granted to CROs/SMOs, so it may be proper to have a contractual relationship with a CRO/SMO instead of a contractual relationship with a Sponsor. The extent of a CRO's/SMO's authority depends on their contract with a Sponsor.

B. STRUCTURE OF THE IRB

1. Composition. The IRB shall have at least five (5) members, with varying backgrounds to promote complete and adequate review of research activities under its review. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of its members including race, gender, cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of Subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law and standards of professional conduct, and practice. The IRB shall therefore include or involve persons knowledgeable in these areas. If the IRB regularly reviews research involving Subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, economically or educationally disadvantaged persons, consideration shall be given to the inclusion or involvement of one or more individuals who are knowledgeable about and experienced in working with these Subjects.

2. Ex Officio Members. Ex officio members of the IRB ("Ex Officio Member(s)") shall be voting members of the IRB for so long as they hold the office or position that qualifies them for membership on the IRB, unless sooner removed as detailed herein. Ex officio members of the IRB shall consist of:

   a. NMH's Vice President of Medical Affairs/Medical Director or designee; and

   b. A Pastoral Representative, who is a chaplain or a member of the ordained clergy in any denomination.

3. Regular Members. Regular voting members of the IRB ("Regular Member(s)") shall include (to the extent these requirements are not already met by the Ex-Officio Members, or in addition thereto):

   a. At least one (1) member whose primary concerns are in non-scientific areas;

b. At least one (1) member whose primary concerns are in scientific areas;

c. At least one (1) member not otherwise affiliated with NMHS, and who is not part of the immediate family of a person affiliated with NMHS;

d. At least one (1) member who is a Registered Nurse affiliated with NMHS;

e. Individuals from more than one (1) profession.

For the purposes of this Handbook, Ex Officio Members and Regular Members are collectively referred to as the "Member(s)" of the IRB.

4. Alternates. Individuals may be appointed as alternate Members of the IRB ("Alternate(s)"), to serve as a voting Member at any meeting or in any specific matter when a Quorum of IRB Members cannot be obtained. Alternate Members shall be appointed by Approval of the IRB or the President of NMH. Alternates are subject to the same training requirements as IRB Members. An Alternate shall have the duties and authority expressly granted to such Alternate.

5. Expert Advice. The IRB, via Approval, or the Chairperson may, at any time, and subject to any applicable non-disclosure requirements, request that research be reviewed by an outside expert (such as a specialty physician or scientist with expertise in a particular facet of the study) with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available to the IRB. Such expert shall not vote with the IRB. The IRB may consider such expert's advice and recommendations when deciding whether to Approve, Disapprove, Conditionally Approve, or Table a study, as each are defined below).

C. APPOINTMENT AND MEMBERSHIP.

1. Appointment. Regular Members of the IRB shall be recommended for appointment by the Chairperson, the President of NMH or a Member of the IRB. Membership to the IRB shall be granted via Approval of the IRB or by the decision of the President of NMH, and upon such Approval or decision, the appointed individual shall constitute a Regular Member.

2. Term. Regular Members shall each serve for a term of three (3) years (a "Term"). Members may be renewed for subsequent Terms upon Approval of the IRB or decision by the President of NMH, during the final year of a Member's Term. The IRB Manager shall maintain a schedule of staggered Terms so the Terms of approximately one-third of the Regular Members are considered for renewal or expiration each year.

3. Maintenance of Records Regarding Members. The Members shall furnish to the IRB Manager information reasonably requested related to education, credentials, licenses, and other professional certifications. The IRB Manager shall maintain a list of the Members, earned degrees, representative capacity (Ex Officio or Regular), board certifications, licenses, and employment or other relationship between each Member and Affiliate.

4. Training. IRB Members are required to undergo periodic training as required by the IRB:

a. Orientation and initial training upon joining the IRB.

b. Informational discussions and news articles provided at IRB Meetings.

c. Periodic Special Meetings with guest speakers on legal/ethical/operational topics.

d. Local, regional or national seminars.

e. Required continuing education or training, as determined by the Chairperson or the President of NMH

e. Online IRB training courses offered by NMH. The IRB Manager or the Chairperson may require that an IRB Member provide documentation of any required training or certification to the IRB Manager. Costs for training covered in this section shall be paid by NMH.

f. Every three (3) years following completion of the initial online IRB training, all IRB Members shall complete a supplemental online IRB training course and provide documentation of successful completion and re-certification to the IRB Manager. The IRB Manager shall track compliance with this requirement.

5. Disqualification of Members; Conflict of Interest. No Member of the IRB shall participate in an IRB vote, review or monitoring (nor be counted toward a Quorum or Approval for such purpose) of any study if:

a. Such Member is or was directly involved in the study under review; or

b. Such Member is directly associated, through family relationship, professional association (partnership or professional corporation) or financial interest, with a Sponsor of a study where IRB action is being taken.

Each of (a) and (b) are referred to in this Handbook as a "Conflict of Interest." A Conflict of Interest shall disqualify a Member from participation in an IRB action, including a vote, Approval, Disapproval, Conditional Approval, or Tabling of any part of a study.

A Member who has a known Conflict of Interest shall disclose such conflict to the IRB or the Chairperson prior to any IRB action related to such conflict. One or more Members of the IRB may be disqualified from participating in an IRB action due to a Conflict of Interest for a given study, though such disqualification shall not impair the ability of the IRB to proceed with the study, provided there is a Quorum (defined below) consisting of Members who are not disqualified by a Conflict of Interest. Any Member having a Conflict of Interest may, in the discretion of the remaining IRB Members, be asked to remain present or be excused during the IRB's deliberations and action subject to the Conflict of Interest.

6. Vacancies. Vacancies on the IRB may be filled by the Chairperson, the President of NMH or Approval by the IRB.

7. Revocation of Membership. Removal of an individual's status as a Regular Member requires either (a) Approval of the IRB, (b) decision of the Chairperson, or (c) decision of

the President of NMH. The decision to remove an individual's status as an Ex Officio Member shall be made by the President of NMH. Any Member subject to removal shall have the right to submit an appeal to the President of NMH. The President of NMH shall then make the final determination for removal.

8. Chairperson. The President of NMH shall appoint a Member of the IRB to serve as Chairperson of the IRB ("Chairperson"). The Chairperson shall have and exercise all duties traditionally held by a committee chairperson or are specifically granted by this Handbook or applicable regulations.

9. Vice Chairperson. The Chairperson may appoint a Member of the IRB to serve as Vice Chairperson of the IRB ("Vice Chairperson"). In the event of the Chairperson's absence, Conflict of Interest, or disqualification, the Vice Chairperson shall assume and discharge the Chairperson's duties. In the event of the Vice Chairperson's absence, Conflict of Interest, or disqualification, the Vice President of Medical Affairs/Medical Director Ex Official Member shall assume and discharge the Chairperson's duties.

D. MEMBER RESPONSIBILITIES

1. Responsibilities. Members shall have the following responsibilities:

   a. Regularly attend IRB Meetings and Special Meetings, as called.

   b. Review materials provided in advance of Meetings as necessary to fully and meaningfully participate in the IRB's actions.

   c. Participate on Subcommittees when appointed by the Chairperson.

   d. Complete training as identified in this Handbook.

   e. Keep private and confidential all documents, discussions and any information acquired in a Member's capacity as a Member.

   f. Disqualify or recuse themselves from action on research where the Member has a Conflict of Interest.

   g. Advise the Chairperson of any concerns regarding IRB operations or any research.

   h. Assist in the identification and development of improved IRB policies and procedures and recommend to the Chairperson any prospective candidates for appointment to the IRB.

   i. Support, promote, and carry out the mission of the IRB to protect human research subjects and the requirements set forth in this Handbook.

   j. Conduct initial and continuing review (at least annually) of research and, if applicable, report the IRB's findings to the Principal Investigator.

   k. Determine which studies require review more often than annually, and which studies need verification from sources other than the Principal Investigator.

l. Ensure prompt reporting to the IRB of proposed changes to a study, and ensure the Investigators conduct their studies in accordance with the terms of the IRB's approval, except where necessary to eliminate immediate hazards to Subjects.

m. Follow written procedures for ensuring prompt reporting to the IRB, NMHS officials, DHHS, or OHRP any (i) unanticipated problems involving risk to Subjects or others or any serious or continuing noncompliance with this Handbook or the FDA Regulations and the Common Rule, and (ii) any suspension or termination of IRB Approval of a study.

E. OPERATIONS

1. Meetings. The IRB shall schedule and hold regular meetings at times and locations to be reasonably determined by the Chairperson (each a "Meeting" and collectively, "Meetings"), usually on a monthly basis. At Meetings, the IRB shall conduct its business as set forth in this Handbook.

2. Special Meetings. Special Meetings may be called by the Chairperson or Approval of the IRB to uphold, maintain and discharge IRB duties (each a "Special Meeting" and collectively, "Special Meetings").

3. Mode of Meetings. The Chairperson shall have the authority to hold exclusively in-person, exclusively virtual, or mixed-mode (allow for both in-person and virtual attendance) Meetings and Special Meetings.

4. Quorum. In order for the IRB to take any action at a Meeting or Special Meeting, including a vote, Approval, Disapproval, Conditional Approval, or Table, or to conduct any IRB-related business, there shall be both a Numerical Quorum and a Compositional Quorum.

   a. Numeric Quorum. A Numerical Quorum shall mean the presence (either in-person or virtually) of a majority of the Members of the IRB, excluding any Member disqualified due to Conflict of Interest.

   b. Compositional Quorum. A Compositional Quorum shall mean the Members present (either in person or virtually) meet the following requirements of the FDA Regulations and the Common Rule:

      i. At least one (1) member whose primary concerns are in non-scientific areas;

      ii. At least one (1) member whose primary concerns are in scientific areas;

      iii. Individuals from more than one (1) profession.

5. Voting and Approval. All actions of the IRB, including a vote, Approval, modification, monitoring or closure of a study, require the affirmative vote of two-thirds (2/3) of Members eligible to vote on the action. Affirmative vote of two-thirds (2/3) of Members eligible to vote shall constitute "Approval" of the IRB. For the purposes of this Handbook, "Approval," "Approved," "Approve," and any other form of the word

"Approve" shall all have the same meaning. Any less than two-thirds (2/3) of Members eligible to vote shall constitute "Disapproval." A vote of the IRB can occur in the following ways:

a. At a Meeting or Special Meeting, with a Quorum. To be eligible to vote, a Member must:

   i. Be present at the Meeting or Special Meeting, whether virtually or in-person;

   ii. Have conducted reasonable review of all documents and information provided to such Member in order for such Member to make an educated and informed decision; and

   iii. Have had the opportunity to ask questions of the Principal Investigator and Sponsor (where applicable), and had the opportunity to deliberate and discuss the applicable action of the IRB with other Members.

b. Via email or electronic communication. The Chairperson may, in taking account all facts and circumstances, authorize any action of the IRB to be taken via email or other electronic communication (referred to as "Electronic Vote"). When the Chairperson authorizes an Electronic Vote, the Chairperson shall provide instruction to the IRB Manager for effectuating the Electronic Vote. At a minimum, an Electronic Vote shall consist of the following:

   i. An email or electronic communication to each Member containing all information and other documents, as determined by the Chairperson, for Members to make an educated and informed decision;

   ii. An email or electronic communication to each Member containing information about how the Members will be voting (for example, via an email reply to the IRB Manager with the words "I Approve");

   iii. Sufficient time for Members to respond to the action, as well as the opportunity to ask questions of the Principal Investigator and Sponsor (where applicable); and

   iv. For the IRB to Approve of an action via Electronic Vote, the IRB Manager must receive an affirmative vote of two-thirds (2/3) of Members eligible to vote.

6. Minutes and Reports. Minutes of all Meetings and Special Meetings of the IRB ("Minutes") shall be taken and preserved reflecting the actions taken at the Meeting. Actions taken via Electronic Vote shall be reported on at the Meeting following such action by the Chairperson, and the report shall be reflected in the minutes. All materials, including supporting and other documents related to studies, modifications, status reports, and closures, as well as correspondences and other communications related to IRB functions, shall become records of the IRB. The IRB shall retain such records in accordance with applicable NMH record retention policies.

7. Authority of Chairperson Between Meetings. The Chairperson, or the Vice Chairperson in the absence of the Chairperson, shall have authority during the period between Meetings of the IRB, either alone or with the assistance of a Subcommittee to take such actions as reasonably necessary to discharge the duties of the IRB, including Approval of Emergency Use and Expedited Review. All actions taken between Meetings shall be reported at the next Meeting and such report shall be reflected in the Minutes.

8. Creation of Subcommittees. The Chairperson, the President of NMH or the IRB (via Approval), shall have the authority to create subcommittees of the IRB ("Subcommittee(s)"). Subcommittees shall conduct the actions it is tasked by the person/entity that created such Subcommittee, and shall only have the authority granted to it by such person/entity. A Subcommittee shall consist of at least three (3) Members.

9. Guidelines and Procedures. The Chairperson, the President of NMH, or the IRB, via Approval, may, at any time adopt additional guidelines, policies, procedures, and criteria for the conduct of its business and for the submission, review and monitoring of studies.

IV. CLASSIFICATION, SUBMISSION, REVIEW, MONITORING

A. DEFINING RESEARCH

1. Scope of the IRB's Authority. All human subject research that:

   a. Is conducted in whole or in part at any Affiliate of NMHS; or

   b. Is under the direction of any employee or agent of an Affiliate of NMHS in connection with institutional responsibilities;

   must first be submitted to the IRB for review and Approval. This includes, but is not limited to, studies for which IRB review is required under regulations of the FDA or HHS. The IRB Chairperson, the President of NMH, or the IRB, via Approval, may also, in each's discretion, accept authority over studies for which IRB review is or is not required under the Common Rule or FDA Regulations. The IRB Chairperson, the President of NMH or the IRB, via Approval, may also, in each's discretion, accept authority over studies in which any of the following are participating:

      i. NMH Medical Staff;

      ii. Employees of NMHS or any Affiliate; or

      iii. Employees separately authorized to render services at any Affiliate of NMHS, and are subject to separate NMH and/or Medical Staff credentialing.

2. Reliance on another IRB. To the extent permitted by the Common Rule and the FDA Regulations, the IRB Chairperson, the President of NMH or the IRB (via Approval) may, accept the review and approval of, or rely on, another qualified IRB.

3. Associate Institutions. The IRB Chairperson, the President of NMH or the IRB, via Approval, may, in its discretion, approve another institution as an affiliate or performance site ("Third-Party Site") for one or more studies under the authority of the IRB. Such approval may authorize the accrual of Subjects at the Third-Party Site, the conduct of study-related activities at Third-Party Site, or the appointment of physicians at Third-Party Site as secondary Investigators. Such approval shall be conditional upon:

   a. The Third-Party Site and the Principal Investigator agreeing to comply fully with all protocols guidelines, standards, policies and procedures established by the IRB and/or Sponsor;

   b. The Third-Party Site agreeing to cooperate fully with the IRB, the Principal Investigator and any applicable affiliate of NMHS in conducting the investigation, reporting data and providing access to records; and

   c. The Third-Party Site executing any other agreements requested by the IRB or legal counsel in connection with a study.

4. Definition of Research. Most of the requirements set forth in the Common Rule and FDA Regulations govern a specific type of research. The Common Rule uses the term

'Research', while the FDA Regulations use the term 'clinical investigation'. For the purposes of this Handbook, the terms 'Research', 'Clinical Investigation', 'Human Subject Research', and 'Study' are collectively referred to as "Research" or "research."

The term "Research" is used broadly herein to refer to both "Human Subject Research" (falling under the jurisdiction of HHS) and "Clinical Investigations" (falling under the jurisdiction of the FDA). Generally speaking, "Human Subject Research" is defined as a systematic investigation, including research, development, testing, and evaluation, designed to develop or contribute to generalizable knowledge, where the investigation:

a. Involves obtaining information or biospecimens about living individuals, and uses, studies, or analyzes the information or biospecimens, either through intervention or interaction with the individuals; or

b. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

This includes everything from data-gathering and analysis only (such as retrospective record reviews, interviews, or questionnaires) to therapeutic research involving investigational drugs, devices, or treatment methods. The term "Clinical Investigation" is defined as any experiment involving a test article and one or more Subjects and either is subject to requirements for prior submission to the FDA, or is not subject to requirements for prior submission to the FDA but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

As a general rule, physicians may, within the scope of their medical license, use any FDA-approved device or FDA-approved drug for any purpose they deem appropriate in the treatment of an individual patient, without IRB review. This general rule is subject to the physician's professional judgment as to what is in the patient's best interest and consistent with acceptable medical standards, licensure, and ethics, subject to any applicable NMHS policies or protocols.

Whether a study constitutes Research (Human-Subject Research or Clinical Investigation) under the law is determined by the Chairperson and IRB legal counsel on a case-by-case basis, taking into account all facts, circumstances, documentation, and other information provided. The Chairperson, the President of NMH, or the IRB (via Approval) may choose to maintain oversight of non-Research, Exempt Research and Excepted Research, as the terms are defined below.

The DHHS and OHRP have published a decision chart to help determine whether a particular activity constitutes research involving Subjects. The IRB Manager or IRB legal counsel can provide such Decision Chart upon request.

As detailed below, some research is exempt or excepted from the Common Rule, FDA Regulations or IRB review requirements. Further, some research may be expedited and not subject to full IRB review.

B. EXEMPT, EXCEPTED AND EXPEDITED RESEARCH

1. General. Whether a study constitutes Exempt Research, Excepted Research, and Expedited Research under the law is made by the Chairperson and IRB legal counsel on a case-by-case basis, taking into account all facts, circumstances, documentation, and other information provided.

2. Excepted Research (Exceptions to Research). Excepted Research meets the definition of Human Subject Research or Clinical Investigation, however the law deems it not to be Human Subject Research or not to be a Clinical Investigation. As such, Excepted Research is not regulated by the Common Rule or FDA Regulations. The following are Excepted Research activities:

   a. Scholarly and journalistic activities collecting information on a specific individual (e.g. oral history, journalism, biography, literary criticism, etc.);

   b. Public health surveillance activities, conducted, supported, requested, ordered, required, or authorized by a public health authority;

   c. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency; and

   d. Authorized operational activities in support of intelligence, homeland security, defense, or other national security missions.

3. Exempt Research. Exempt Research meets a definition of Research but is considered by the Common Rule or FDA Regulations to be 'exempt' from some, most, or all of the requirements under the law. Exempt Research typically has special rules that must be followed. The following activities are Exempt Research:

   a. Research conducted in established or commonly accepted educational settings that specifically involves normal educational practices not likely to adversely impact students (e.g. regular/special education, instructional techniques, curricula, or classroom management methods).

   b. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior and meets at least one of the following criteria:

      i. The information obtained is recorded such that the identity of the Subject cannot readily be ascertained, directly or through identifiers linked to the subjects;

      ii. Any disclosure of the Subject responses outside the research would not reasonably place the Subject at risk of criminal or civil liability or be damaging to the Subject financial standing, employability, educational advancement, or reputation;

      iii. The information obtained is recorded by the investigator in such a manner that the identity of the Subject can readily be ascertained,

directly or through identifiers linked to the Subject and an IRB conducts a limited IRB review as required by applicable law.

c. Research involving benign behavioral interventions (brief in duration, harmless, painless, not physically invasive) & the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording and if at least one of the following criteria is met:

   i. The information obtained is recorded that the identity of the Subject cannot readily be ascertained, directly or through identifiers linked to the subjects;

   ii. Any disclosure of the Subject responses outside the research would not reasonably place the Subject at risk of criminal or civil liability or be damaging to the Subject's financial standing, employability, educational advancement, or reputation;

   iii. The information obtained is recorded by the investigator in such a manner that the identity of the Subject can readily be ascertained, directly or through identifiers linked to the Subject.

d. "Secondary Research" for which consent is not required (Secondary Research is research using identifiable private information or identifiable biospecimens) and if at least one of the following criteria is met:

   i. The identifiable private information or identifiable biospecimens are publicly available;

   ii. Information is recorded by the investigator in such a manner that the identity of the Subject cannot readily be ascertained, the investigator does not contact the Subject, and the investigator will not re-identify the Subject (for example, retroactive chart review);

   iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when use is regulated under HIPAA;

   iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information.

e. A project or demonstration conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency, and are designed to study, evaluate, improve, or otherwise examine public benefit or service programs.

f. A taste and food quality evaluation or consumer acceptance study.

g. Research for storage or maintenance for secondary research for which broad consent is required.

h. Secondary Research for which broad consent is required under HIPAA. That is, Research involving the use of identifiable private information or identifiable biospecimens for Secondary Research use, if all of the following criteria are met:

i. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens;

ii. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with the Common Rule; and

iii. An IRB conducts a limited IRB review and determines that the research to be conducted is within the scope of the broad consent.

4. Expedited Review and Research. "Expedited Research" is research involving minimal risk to Subjects. "Expedited Review" is the Chairperson or other person designated by the Chairperson's review of minor changes in previously Approved research that constitute minimal risk to Subjects. Minimal risk means that the probability and magnitude of harm or discomfort anticipated is not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Minimal risk is further defined below.

Expedited Research may be reviewed and approved by the Chairperson without full IRB approval. At the IRB Meeting following the Chairperson's action related to Expedited Research, the Chairperson shall report such action to the full IRB, which may ratify, reverse or modify the Chairperson's expedited actions. The Chairperson may decline to approve Expedited Research and refer the matter for full IRB review. The IRB shall be given sufficient time to review such Expedited Research before voting to Approve. Under the Common Rule and FDA Regulations, declining to approve a study requires action by the full IRB. Expedited Research is Subject to the same reporting requirements (annual reviews, modifications, adverse events) as other studies.

OHRP has provided the following guidance on Expedited Research:

The Expedited Review process may not be used where identification of the Subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the Subject's financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The Expedited Review process may not be used for classified research involving Subjects.

The standard requirements for informed consent (or its waiver, alteration, or exception) apply.

Research may be reviewed by the IRB through the Expedited Review process if it:

a. Presents no more than minimal risk to subjects; and

b. Involves only procedures listed in one or more of the categories listed below. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to Subjects. The categories in this list apply regardless of the age of Subjects, except as noted.

Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Research Categories Eligible for Expedited Review:

i. Clinical studies of drugs and medical devices only when condition (A) or (B) is met.

A. Research on drugs for which an investigational new drug application is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

B. Research on medical devices for which (i) an investigational device exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

ii. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

A. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

B. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

iii. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) un-cannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of

the membrane prior to or during labor; (h) supra- and sub- gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

iv. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

v. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of Subjects. This listing refers only to research that is not exempt.)

vi. Collection of data from voice, video, digital, or image recordings made for research purposes. In the case of electronic data, the decision for expedited review will depend on the specific structure and circumstances of the Study.

vii. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of Subjects. This listing refers only to research that is not exempt.)

viii. Continuing review of research previously approved by the convened IRB as follows:

A. Where (i) the research is permanently closed to the enrollment of new Subjects; (ii) all Subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of Subjects; or

B. Where no Subjects have been enrolled and no additional risks have been identified; or

C. Where the remaining research activities are limited to data analysis.

ix. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

C. COMPASSIONATE USE, EMERGENCY USE, HUMANITARIAN DEVICE.

1. General. The terms “Compassionate Use,” “Emergency Use,” “Humanitarian Device,” “Treatment Investigational New Drug,” and other similar terms (collectively referred to herein as “Compassionate Use”) are often used within the medical and research communities to describe the use of an investigational drug, devise or other therapy for a single patient or a few patients who have a terminal illness or are experiencing a medical emergency and have no other viable treatment options. Physicians or other healthcare providers may contact the IRB or the Chairperson for approval of Compassionate Use of a drug, device, or other therapy. The term "Compassionate Use" is not formally recognized in the Common Rule or FDA Regulations, and therefore has no legal meaning on its own; neither the IRB nor the Chairperson have approval authority on this basis alone.

2. Types of Uses Considered Compassionate. The following situations are those which are typically identified as Compassionate Uses:

a. Emergency Use. Emergency Use is defined as the use of a test article on a Subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. Test Article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food, Drug and Cosmetic Act or under sections 351 or 354-360F of the Public Health Service Act.

The FDA Regulations allow for Emergency Use of a Test Article to be used in emergency situations without prior IRB approval, provided the use is reported to the IRB within five (5) working days and subsequent uses of the same Test Article are reviewed by the IRB.

Any provider using an investigational drug on an Emergency Use basis must notify the IRB Manager or Chairperson within five (5) working days. The IRB Manager or Chairperson will promptly notify the IRB via electronic communication.

Should a situation arise which would require the Emergency Use of the Test Article for a second patient, either by the same or a second physician, or the same Test Article, subsequent Emergency Use should not be withheld for the purpose of gaining IRB approval. If it appears probable that similar emergencies will require subsequent use of the Test Article at the institution, every effort should be made either to sign on to the applicable Sponsor's Protocol or to develop a Protocol for future Emergency Use of the Test Article. Either of these Protocols would need to be prospectively reviewed and approved by the IRB for future use of the Test Article.

In Emergency Use circumstances, it may not be feasible to obtain informed consent prior to using the Test Article. The FDA Regulations provide an exemption from the informed consent requirement for such situations. Emergency Uses qualifying for this exemption are defined as:

i. Life-threatening situations necessitating use of the Test Article;

ii. Where the Subject is unable to provide effective consent;

iii. There is insufficient time in which to obtain consent from the Subject's legal representative; and

iv. There is no available alternative method of approved or generally recognized therapy of equal or greater likelihood of saving the Subject's life.

Special procedures for documenting the infeasibility of obtaining consent apply as follows: The Principal Investigator and an unaffiliated physician who has no relation to the Emergency Use or the drug must certify in writing the existence of all four conditions listed above before use of the Test Article. If in the Principal Investigator's opinion, immediate use of the Test Article is necessary to save the life of the Subject and there is insufficient time to obtain IRB Approval or other independent determination required by the FDA Regulations before using the Test Article, the Principal Investigator is to make written determinations, then obtain the written review and independent evaluation from such unaffiliated physician within five (5) working days after the use of the Test Article. The documentation required to be submitted to the IRB must also be submitted. Legal counsel may be consulted, and the Test Article manufacturer/vendor may be contacted.

The use of a Test Article in an investigation designed to be conducted under emergency conditions (e.g., emergency room research) usually does not qualify for an Emergency Use designation on its own.

b. Humanitarian Use Device. “Humanitarian Device Exemption” or “HDE” means a premarket approval application submitted pursuant to this subpart seeking a

humanitarian device exemption from the effectiveness requirements of ordinary FDA approval.

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

In some cases the FDA will grant a Humanitarian Device Exemption or HDE to a new medical device to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in not more than 8,000 individuals in the United States per year. These devices are known as Humanitarian Use Devices or HUD(s). Use of an HUD under an HDE initially requires full IRB review and Approval (not expedited review).

The usual informed consent requirements do not apply to HUD's if the device is not being used in a research study. However, the IRB may still require part of all of the informed consent requirements. Continuing review following initial IRB Approval may be Expedited by the Chairperson.

c. Single Patient Use. A "Single Patient Use" allows a physician to obtain access to an investigational drug for the treatment of a single patient. A patient who meets this criteria is in a desperate situation and unresponsive to other therapies, or in a situation where no approved or generally recognized treatment is available. There may be little evidence that the proposed therapy is useful, but it may be plausible based on theoretical grounds or anecdotes of success. Access to investigational drugs for use by a single, identified patient may be gained either through a Sponsor under a treatment protocol; or through the FDA, by first obtaining the drug from Sponsor, and then requesting from the FDA authorization to use the investigational drug for treatment use. This type of use does not require IRB notification, Approval, or follow- up review.

d. Treatment IND. A "Treatment IND" is a treatment Protocol added to an existing investigational new drug ("IND") application, which allows physicians to treat qualifying patients according to the Protocol, and which provides additional data on the drug's safety and effectiveness.

Treatment IND's are available for patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapy exists. Treatment INDs require full prospective IRB review and Approval in the same manner as other clinical studies, unless local IRB review is specifically waived by the FDA.

3. Limited Authority of IRB Chairperson. The Chairperson does not have the authority to unilaterally grant Approval to any Compassionate Use without full IRB review and Approval. However, the IRB Chairperson may:

a. Receive reports of Emergency Uses, and report use to the IRB at its next Meeting.

b. Assist an Investigator or physician, whichever applicable, in determining which category applies to the proposed Compassionate Use, and therefore, which procedures to follow.

c. Assist in bringing before the IRB those matters that require IRB approval.

D. SECONDARY SITE STUDIES.

1. Defined. "Secondary Site Studies" refer to studies that have already been or will be subject to full review and approval by an IRB other than the IRB, and in which:

a. Limited study activity will occur at an Affiliate of NMHS, such as tissue collection or record-keeping; or

b. Physicians at an Affiliate of NMHS have been asked to accrue and consent patients at such Affiliate of NMHS to participate in the study entirely at the other institution's site.

2. Approval. The Chairperson may accept Secondary Site Studies and waive the requirement of Approval by the IRB, under the following conditions:

a. The Investigator(s) must submit to the IRB Manager or Chairperson:

i. A written summary of the study satisfactory to the Chairperson,

ii. The Protocol under which the study is being conducted at the supervising institution,

iii. Documentation from the supervising IRB that the Protocol has been approved, the study is being conducted under the supervision of the supervising IRB, the Investigators have been approved by the supervising IRB to act as Investigators, and

iv. The ICF (defined below) must clearly authorize the activity which will occur at an Affiliate of NMHS and must comply with IRB standards for informed consent and HIPAA Authorization. The Chairperson may condition approval of Secondary Site Studies on revisions to the ICF. The Chairperson may bring applications for Secondary Site Studies to the IRB for Approval.

Secondary Site Studies may differ in their respective order of events. As such, the Chairperson has the authority to work with Secondary Site Study Investigators to come to a mutually agreeable solution for achieving the above conditions.

b. Ongoing Obligations. The Investigator(s) must agree to furnish the Chairperson with any follow-up information presented to or developed by the supervising IRB, and must agree to notify the Chairperson immediately if the study is terminated, curtailed, or amended, or if any Investigator's status as an Investigator is terminated, curtailed, or amended by the supervising IRB.

c. The Investigator(s) must have necessary privileges through normal Medical Staff channels commensurate with their planned activities at the Affiliate of NMHS.

d. The Investigator(s) must agree to appear before Meetings of the IRB if requested, and furnish the Chairperson or the IRB with such reports or additional information as are requested, from time to time.

e. Upon receipt of all required information, the Chairperson may accept Secondary Site Studies, subject to any limitations or conditions the Chairperson deems appropriate. All actions taken by the Chairperson related to Secondary Site Studies shall be reported to the IRB at the next Meeting, and the IRB shall have authority to rescind, withdraw or modify the Chairperson's actions.

E. SUBMISSION AND REVIEW OF NEW STUDIES

1. General. Before undertaking a study, an Investigator shall submit a complete application to the IRB Manager for the IRB's review (a "New Study Application"). The IRB Manager and Chairperson shall establish a template for New Study Applications. Along with a New Study Application, the Investigator shall include, at a minimum, an investigational plan, research plan, or Protocol, a report of prior investigations or research, a proposed ICF, and such additional information as the IRB may require, the Investigator may deem appropriate, or as required by the Common Rule or FDA Regulations. Investigators may request a copy of this Handbook prior to submission of a New Study Application.

2. Procedure for Submission of New Studies.

a. The New Study Application shall be submitted to the IRB Manager. In general, New Study Applications submitted prior to the second Monday of the month will be reviewed by the IRB at Regular Meeting that same month. New Study Applications submitted after such date will be reviewed at the subsequent month's Regular Meeting. The New Study Application must be completed in full, signed by the Investigator, and accompanied by:

i. The complete study Protocol and any amendments to date, together with reports of prior investigations and Sponsor approval reports/letters.

ii. The proposed ICF.

iii. For any listed Investigators, such Investigator's complete and current curriculum vitae, licensing information, and evidence of completion of IRB-required training.

iv. A Financial Disclosure Form (FDF) and/or Form 3454, 1572, if applicable.

v. National Clinical Trial Code (NCT), if applicable.

vi. Any recruiting or other materials that Subjects will be given.

vii. Any other information requested by or on behalf of the IRB.

viii. Any other information the Investigator deems helpful.

b. The Principal Investigator, another Investigator or a designee of Principal Investigator, acceptable to the Chairperson, shall attend the Meeting at which the New Study Application is being reviewed by the IRB. The Investigator(s) in attendance shall provide an overview and explanation of the study and answer questions of the IRB.

3. Informed Consent Form. In conjunction with submission of a New Study Application, or at another time as permitted by the Chairperson, a Sponsor shall submit to the IRB a proposed Informed Consent Form ("ICF") for a Study. IRB legal counsel shall review and negotiate any such ICF prior to Approval of a New Study Application by the IRB. Each ICF shall meet the ICF requirements as set forth in this Handbook.

4. Waiver, Alteration. The IRB may waive the ICF requirement, or alter the requirements of an ICF, by way of Approval, if permitted under the FDA Regulations or the Common Rule, as applicable, and the IRB determines that:

a. The study involves no more than minimal risk to the Subjects;

b. The Study could not practicably be carried out without the requested waiver or alteration;

c. If the study involves using identifiable private information or identifiable biospecimens, the Study could not practicably be carried out without using such information or biospecimens in an identifiable format;

d. The waiver or alteration will not adversely affect the rights and welfare of the Subjects; and

e. Whenever appropriate, Subjects will be provided with additional pertinent information after participation.

5. Criteria for Assessing New Study Applications. In considering whether to Approve, Conditionally Approve, Disapprove, or Table (as each are defined below) a proposed study, the IRB shall consider, without limitation:

a. Whether the information submitted to the IRB concerning the study contains any untrue statement of a material fact or omits material information required by the IRB, the Common Rule or the FDA Regulations;

b. Whether the report of prior investigations or research is adequate to support a conclusion that it is reasonably safe to begin the proposed study;

c. Whether there is reason to believe the device, drug, treatment or procedure that is the part of the study may be unsafe or ineffective when used for the purpose or in the manner for which it is to be investigated;

d. Whether the study plan or Protocol is a reasonable plan for a scientific study to serve the stated purposes of the study;

e. Whether the proposed study conforms to procedures, conditions, and requirements prescribed by the IRB and applicable laws and regulations;

f. Whether the proposed study exposes individuals to undue risks. Risks considered include, but are not limited to, physical and psychological risks, social risks (such as risk to privacy interests), economic risks (including direct and indirect costs to the patient), and legal risks. In assessing risks, the IRB shall consider, among other things, whether:

    i. Whether the risks to Subjects are minimized (A) by using procedures consistent with sound research design and that do not unnecessarily expose Subjects to risk, and (B) whenever appropriate, by using procedures already being performed on the Subjects for diagnostic or treatment purposes;

    ii. Whether the risks to Subjects are reasonable in relation to the anticipated benefits, if any, to Subjects and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility;

g. Whether the selection of Subjects is equitable, taking into account the purposes of the research and the setting in which the research will be conducted;

h. Whether informed consent will be sought from each prospective Subject or the Subject's legally authorized representative, in accordance with, and to the extent required by the Common Rule, FDA Regulations, and applicable NMHS policies and procedures;

i. That informed consent is appropriately documented or appropriately waived in accordance with the Common Rule and FDA Regulations;

j. When appropriate, the research plan or Protocol makes adequate provision for monitoring the data collected to ensure the safety of Subjects;

k. When appropriate, that there are adequate provisions to protect the privacy of Subjects and to maintain the confidentiality of data;

l. Whether provision has been made in the study or by the IRB or others for prompt reporting to the IRB, the Investigator, appropriate NMHS officials, the FDA, HHS, and/or the Sponsor, of:

    i. Unanticipated problems involving risks to Subjects or others,

ii. Information received concerning injuries to Subjects,

iii. Any changes in the study which are reviewed and approved by the IRB,

iv. Any instance of serious or continuing noncompliance with the Common Rule or FDA Regulations, or with the requirements or determinations of the IRB,

v. Any suspension or termination of IRB approval, or

vi. Drug or device deficiency problems.

m. Whether any aspect of the proposed study presents possible Conflicts of Interest, and if so, whether there are appropriate safeguards to prevent or minimize any impact of such Conflicts of Interest on the conduct of the study. Potential Conflicts of Interest to be considered shall include, but are not limited to, significant financial interests of the Investigator in the research and Conflicts of Interest that may be created by the payment of fees or other benefits to the study Subject.

n. When some or all of the Subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, whether additional safeguards have been included in the study to protect the rights and welfare of these Subjects.

When the IRB is permitted by law to conduct a limited review for storage or maintenance for Secondary Research, the IRB shall make the following determinations instead of those in (a) through (n) above:

o. Broad consent for storage, maintenance, and Secondary Research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements in this Handbook;

p. Broad consent is appropriately documented or waiver of documentation is appropriate; and

q. If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of Subjects and to maintain the confidentiality of data.

6. Approval, Conditional Approval, and Disapproval of New Study Applications. Based upon the New Study Application, the Investigator's presentation to the IRB and answering of questions, the IRB's review pursuant to this Handbook, investigational, study plan/Protocol, the report of prior investigations or research and such other information as the IRB considers relevant, the IRB shall either Approve, Conditionally Approve, Disapprove, or Table a study. The IRB may request additional information if it

does not believe it has adequate information on which to base a decision, and may Table any study pending receipt of information.

a. Approval. Approval of New Study Applications shall comply with voting, quorum, and other conditions for Approval as discussed in this Handbook. Approval shall entitle the Investigators to participate in the study subject to any conditions or modifications imposed by the IRB. Such conditions or modifications must also be approved by the Sponsor, when applicable. Unless otherwise specified by the IRB, Approval by the IRB is effective immediately, subject to the authority of the President of NMH to revoke approval or impose additional conditions or modifications. Approval to accrue patients at an Affiliate shall be subject to any additional conditions or authorizations required by the Sponsor and the Affiliate, if applicable.

b. Disapproval. Failure to obtain sufficient votes for Approval shall constitute Disapproval. Upon Disapproval, the Investigator shall not proceed with the study at NMHS or any Affiliate. The Investigator may request reconsideration and may submit additional information to the IRB.

c. Conditional Approval. An Approval by the IRB may be accompanied by conditions. Such conditions may include, but are not limited to, changes to the informed consent document, changes to the Protocol, and changes to marketing materials or other distributions to potential Subjects. IRB Approval with conditions constitutes "Conditional Approval," and the IRB's action shall not constitute Approval until such conditions are met.

d. Table. The IRB may decide, with the vote of two-thirds (2/3) of Member eligible to vote, to table a New Study Application ("Table") for any reason as determined by the IRB. When a New Study Application is Tabled, the study shall be deemed neither Approved or Disapproved. When a study is Tabled, no Subjects shall be enrolled in the study and no action should be taken to further NMHS or an Affiliate's involvement in the Study until the IRB holds another vote to determine the fate of the study.

7. Report. Where the IRB has Approved or Conditionally Approved a New Study Application, the IRB Manager shall forward to the Investigator, or another person or entity as designated by the Chairperson, a written report of the IRB's actions and any conditions imposed. A copy of this Handbook shall be provided to all Investigators of New Study Applications that have been Approved. A Study shall not commence until all Investigators have reviewed this Handbook and agreed to its terms. The IRB may correspond or deal directly with Medical Staff or other NMH officials, the Sponsor, the FDA, and/or HHS in having outstanding questions answered or resolving conflicts regarding the scope of Approval.

8. IRB Fees. In order to defray administrative costs, and consistent with generally accepted IRB practices, the IRB has set and will continue to set, via annual Approval, a fee schedule ("Fee Schedule") for fees for the IRB's services ("Fee(s)"). Fee may be waived for studies Sponsored by nonprofit companies or local physician-Investigators, as determined on a case-by-case basis by the IRB and as communicated in writing. The Chairperson and the President of the NMH shall resolve any question as to whether a Fee applies to a particular Study. Fees are due promptly following review of a New Study

Application, or as otherwise determined by the Chairperson. The Fee Schedule shall set forth any Fees that may be refunded if a Study is Disapproved. Unless otherwise determined by the Chairperson and the President of NMH, no part of a Fee is refundable (including studies that have been suspended where Approval has been revoked).

9. Clinical Trial Agreements, Contracts, Non-Disclosure Agreements, Informed Consent Forms.

   a. Non-Disclosure Agreements. At any time prior to submission of a New Study Application or Study-related documentation, a Sponsor may submit to NMHS legal counsel a proposed Non-Disclosure Agreement or other agreement draft covering matters of confidentiality. IRB legal counsel shall review and negotiate any such agreement prior to receipt of a New Study Application or Study-related documentation.

   b. Clinical Trial Agreements. At any time prior to submission of a New Study Application, a Study Sponsor may submit to the IRB a proposed Clinical Trial Agreement or other agreement governing the relationship between the Sponsor, NMH, the Investigators, and a contract research organization (as applicable). IRB legal counsel shall review and negotiate any such agreement prior to Approval of a New Study Application by the IRB.

10. Study Phases. Some studies are categorized by phase, depending on several factors, including whether the intervention has been tested on human subjects before. While the term is commonly used in the industry of clinical research, the term 'phase' can vary in meaning. The term shall be used for generalization purposes, but shall not be relied upon. Clinical research 'phases' are generally described by the FDA below:

    Phase 1:

    Study Participants: 20 to 100 healthy volunteers or people with the disease/condition.

    Length of Study: Several months

    Purpose: Safety and dosage

    During Phase 1 studies, researchers test a new drug in normal volunteers (healthy people). In most cases, 20 to 80 healthy volunteers or people with the disease/condition participate in Phase 1. However, if a new drug is intended for use in cancer patients, researchers conduct Phase 1 studies in patients with that type of cancer.

    Phase 1 studies are closely monitored and gather information about how a drug interacts with the human body. Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are.

    As a Phase 1 trial continues, researchers answer research questions related to how it works in the body, the side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits. This is important to the design of Phase 2 studies.

    Approximately 70% of drugs move to the next phase

Phase 2:

Study Participants: Up to several hundred people with the disease/condition.

Length of Study: Several months to 2 years

Purpose: Efficacy and side effects

In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial.

Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.

Approximately 33% of drugs move to the next phase

Phase 3:

Study Participants: 300 to 3,000 volunteers who have the disease or condition

Length of Study: 1 to 4 years

Purpose: Efficacy and monitoring of adverse reactions

Researchers design Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants.

Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects

Approximately 25-30% of drugs move to the next phase

Phase 4:

Study Participants: Several thousand volunteers who have the disease/condition

Purpose: Safety and efficacy

Phase 4 trials are carried out once the drug or device has been approved by FDA during the Post-Market Safety Monitoring

F. CONTINUING REVIEW AND MONITORING

1. Status Report, Form. The IRB shall conduct ongoing review for each Approved study at least one time annually (each review, a "Status Report"). The requirement for ongoing review shall continue until the study is closed at NMHS.

2. Ongoing Review Waived. The IRB need not conduct ongoing review of a study in the following circumstances:

    a. Research eligible for Expedited Review;

    b. Research reviewed by the IRB in the form of a Limited IRB Review;

    c. Research has progressed to the point that it involves only one or both of the following, which are part of an IRB-Approved study:

        i. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

        ii. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

    For ongoing reviews that meet the above criteria for waiver, the IRB may opt, via Approval, to require a Status Report.

3. Procedures for Status Reporting. Investigators or Sponsors shall submit a completed Status Report Form to the IRB Manager, together with any additional information as requested by the IRB, in no event later than two weeks prior to the IRB meeting immediately prior to each one-year anniversary of a study's Approval date. The IRB may request more frequent submissions of the Status Report Form. In the event of Investigator or Sponsor's failure to submit a timely Status Report Form or late submission of such form, the IRB may, via Approval, revoke its Approval of a study or suspend study-related activity at NMH.

    Following the IRB's receipt of a completed Status Report Form, the IRB shall review such form along with any additional information submitted, and determine whether to Approve continuation of the study or take other action as determined by the IRB via Approval.

    The IRB may opt to Approve, Disapprove, Conditionally Approve, or Table a Status Report in the same manner as it would for a New Study Application.

G. MODIFICATIONS.

1. Request for Modification. The IRB must review and Approve any modification to a study (each, a "Modification"), including, but limited to, Modifications to the Protocol, ICF or materials distributed to Subjects.

2. Procedures for Modifications. Investigators or Sponsors shall submit a completed Request for Modification Form to the IRB Manager, together with any additional information as requested by the IRB, at least two weeks prior to the IRB meeting that the Investigator or Sponsor wishes the IRB to review a Modification. The IRB shall make

reasonable efforts to review Modifications in a timely manner. Modifications shall not be implemented without IRB Approval.

The IRB may opt to Approve, Disapprove, Conditionally Approve, or Table a Modification in the same manner as it would for a New Study Application.

The Request for Modification Form may also be used to request reactivation of a study which was previously Approved, was suspended, and is now being proposed for reactivation.

For proposed Modifications that are only editorial or grammatical, or do not affect the risk-benefit analysis of a study, the Chairperson may approve the Modification via Expedited Review.

H. PROTOCOL DEVIATION.

1. Protocol Deviations. The IRB must Approve any change, deviation or alteration from the procedures set forth in a Protocol (each, a "Deviation").

2. Procedures for Deviations. The Investigators or Sponsors shall submit Deviations to the IRB Manager using the Protocol Deviation Report Form. Deviations can be either Proactive or Retroactive. Proactive Deviations are Deviations submitted to the IRB prior to the occurrence of the Deviation. Retroactive Deviations are Deviations submitted to the IRB after the occurrence of the Deviation.

   The IRB may opt to Approve, Disapprove, Conditionally Approve, or Table a Deviation in the same manner as it would for a New Study Application.

3. Proactive Deviations. Proactive Deviations shall be submitted to the IRB Manager at least two weeks prior to the IRB meeting that the Investigator or Sponsor wishes the IRB to review the Deviation. The IRB Chairperson shall review each Deviation submission. For Proactive Deviations that do not affect the risk-benefit analysis of a study, the Chairperson may approve the Deviation via Expedited Review. All other Proactive Deviations shall be subject to Approval by the IRB. The Principal Investigator shall ensure a Proactive Deviation is reported to the Sponsor, as applicable.

4. Retroactive Deviations. Retroactive Deviations shall be submitted to the IRB Manager promptly after becoming aware of the occurrence of the Deviation. The IRB Chairperson shall promptly review each Deviation submission. The IRB Chairperson shall have the authority to suspend study related activities following a Deviation until the next IRB Meeting. All Retroactive Deviations shall be reported to the IRB at the IRB meeting following the IRB Manager's receipt of a Deviation submission. The IRB shall review all Retroactive Deviations to determine, via Approval, whether to permit a study to continue.

I. ADVERSE EVENTS; UNANTICIPATED PROBLEMS.

1. Adverse Events. The IRB must review and Approve any adverse events that occur during a study (each, an "Adverse Event"). Generally, an Adverse Event is any untoward or unfavorable medical occurrence in a Subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the Subject's participation in a study, whether or not considered related to

the Subject's participation in a Study. A Sponsor may have their own definition of Adverse Event that requires reporting to it and IRB Approval. Adverse Events are generally classified as either Internal or External.

a. Internal Adverse Event. An Internal Adverse Event is one where an adverse event is experienced by Subjects enrolled by an Investigator at any Affiliate of NMHS. In the context of a single-center clinical trial, all adverse events are considered Internal Adverse Events.

b. External Adverse Event. An External Adverse Event is one where an Adverse Event is experienced by a Subject enrolled by an Investigator at another institution engaged in the study, or a Subject in a different study with the same study-related interventions experiences an Adverse Event.

2. Procedures for Adverse Events. Investigators or Sponsors shall submit a completed Adverse Event Form to the IRB Manager, together with any additional information as requested by the IRB, promptly after the Adverse Event occurs and in compliance with any applicable terms in a Protocol. Unless otherwise directed by the Sponsor or the IRB Chairperson, the study may continue pending IRB review of follow-up modifications.

a. Specific Procedures for External Adverse Events. External Adverse Events are not required to be routinely submitted to the IRB for review. The IRB acknowledges that the Sponsor is in a better position to assess the implications and significance of External Adverse Event information from multiple sites and to make a determination about whether an External Adverse Event shall be reported to the IRB. Accordingly, the Investigator may rely on the Sponsor to determine which, if any, External Adverse Events shall be reported to the IRB. For those External Adverse Events that the Sponsor has determined require a Modification, such Modification shall be shall be submitted as described in the Modification section of this Handbook.

b. Specific Procedures for Internal Adverse Events. Internal Adverse Events shall be promptly reviewed by the Chairperson. For Internal Adverse Events that do not pose more than minimal risk to Subjects, the Chairperson shall have the authority to approve continuation of the study. For Internal Adverse Events that pose more than minimal risk to Subjects, the IRB shall review and Approve continuation of the study.

3. Unanticipated Problems.

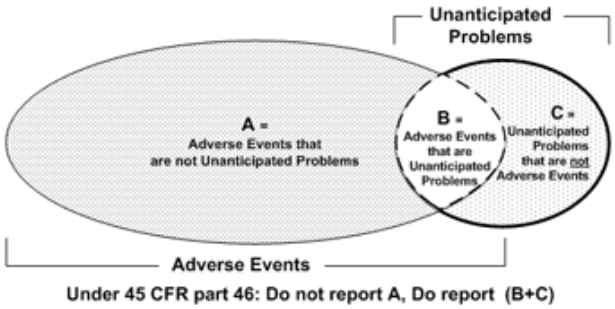
a. Defined. "Unanticipated Problem(s)" are any incidents, experiences, or outcome that meet all of the following criteria:

i. Are unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the Protocol-related documents, such as the IRB-approved research Protocol and ICF, and (b) the characteristics of the subject population being studied;

ii. Are related or possibly related to participation in the research; and

iii. Suggest that the research places Subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Not all Adverse Events are Unanticipated Problems. OHRP has provided the following graphic to explain the relationship between Adverse Events and Unanticipated Problems:



Under 45 CFR part 46: Do not report A, Do report (B+C)

b. Procedures. Unanticipated Problems generally warrant consideration of substantive changes in the Protocol and/or ICF or other corrective actions in order to protect the safety, welfare, or rights of Subjects or others. All Unanticipated Problems shall be promptly reported to the Chairperson and the IRB Manager by the Investigator or Sponsor. A report of Unanticipated Problems shall contain the following information:

i. Specific details regarding the incident, experience or outcome at issue;

ii. A detailed description of how such incident, experience or outcome meets the definition of an Unanticipated Problem.

The Chairperson, the President of NMH, and IRB legal counsel shall determine whether to report an Unanticipated Problem to OHRP. If it is determined that an Unanticipated Problem is to be reported to OHRP, such report shall be made promptly by the President of NMH and legal counsel.

J. CLOSURES

1. Closures. The IRB must review and Approve any closure of a study at NMH (each, an "Study Closure"). Study Closures are categorized as either "To Accrual" or "Permanent."

a. To Accrual. A "Study Closure to Accrual" occurs when a Sponsor informs NMH (or an Investigator) that accrual goals have been met and have instructed participating institution's to stop enrolling new Subjects.

b. Permanent. A Permanent Study Closure is the conclusion of study-related activities at NMH. All Study Closures shall be reported, regardless of the reason for closure, to the IRB.

2. Procedures for Closures. Investigators or Sponsors shall submit a completed Study Closure Form to the IRB Manager, together with any additional information as requested by the IRB, promptly after an event causing such Study Closure occurs. The IRB may opt to Approve, Disapprove, Conditionally Approve, or Table a Study Closure in the same manner as it would for a New Study Application. The IRB Manager shall issue documentation of the IRB's actions to the applicable Investigator and Sponsor.

K. MATERIALS. All advertisements, bulletins, Subject recruitment materials, Investigator brochures, and public promotions of a study under IRB review which are directed to Subjects or potential Subjects are considered to be an extension of the ICF process, and must be specifically Approved by the IRB before being used. Advertisements directed to a potential Subject's referring physician and other scientists, nurses, and administrative staff do not require IRB Approval, but may be subject to review and Approval by the IRB at the discretion of the Chairperson.

L. CASE REPORT, SERIES, PUBLICATION. All case reports or series, or other publishable material generated through the review of Subject data shall be submitted to the IRB for review and must Approved by the IRB before being made available to the public.

M. MISCELLANEOUS REPORTS. Any other communication from Investigators or Sponsors to the IRB may be transmitted via the Miscellaneous Reporting Form.

N. IRB's RESPONSIBILITIES.

1. As part of the IRB's responsibilities in Subsections (A) through (M), the IRB shall:

a. Investigate all matters specified in Subsections (A) through (M) coming to the attention of the IRB, including complaints from Subject, other NMH patients, family, members of the Medical Staff or others;

b. Compare the actual results of a study with the description of anticipated results contained in the study plan; and

c. Require that the Investigator periodically, and not less frequently than annually, according to a schedule to be determined by the IRB for each study, certify to the IRB that:

i. All reports required to be completed by the Investigator and filed with the Sponsor, the FDA, HHS, and the IRB are being completed and filed;

ii. Informed consent is being obtained from or on behalf of all Subjects involved in the study and properly documented as part of the study; the IRB may, in its discretion, audit the Investigator's consent records, and may observe or have a third party observe the consent process in any case;

iii All other documentation required by the IRB is being obtained and maintained by the Investigator;

iv. The conditions, if any, attaching to the IRB's approval or the FDA or HHS approval are being adhered to;

v. The study is proceeding within any guidelines established by the sponsor, and the sponsor/Investigator relationship continues to be in effect; and

vi. There are not, to the knowledge of the Investigator, any new studies, test results or data that, if available and included within the original submission to the IRB, would have required the IRB to Disapprove the study or to place new or different conditions upon the study.

2. IRB Policy on Re-Consenting. The IRB shall determine, in any case where a report of Modification, Adverse Event, or other information indicates a change in risk or benefit, and/or whether the ICF must be changed. If it is determined the ICF must be changed, and if there are Subjects enrolled locally, the IRB shall determine, via Approval, whether re-consenting of the locally enrolled Subjects is to be performed. In the case of an Expedited Review, the Chairperson shall determine whether re-consenting of locally enrolled Subjects is to be performed. Subjects determined by this process to require re-consenting shall be promptly notified of the material new information, including all newly identified risks, and/or re-consented, as most appropriate in each case. In the case of newly identified, life-threatening risks that are likely related to the study, the IRB or Chairperson may direct that enrolled Subjects be re-consented as promptly as reasonably possible. In each case, the decision whether (and how) to notify or re-consent Subjects shall be based on the apparent overall best interest of the Subjects enrolled and the reasonableness of notification or re-consenting under the circumstances.

3. Investigator's Responsibility. The Investigator shall submit timely and complete reports to the IRB as described in this Handbook. The Investigator is responsible for notifying the IRB whenever approval of the study or Investigator is withdrawn by the Sponsor, FDA, or HHS. Additionally, the Investigator shall notify the IRB in the event the Investigator discontinues the study at any time other than the scheduled completion date. In the event the FDA releases a device or drug which is the subject of a study from its designation as an investigational device or drug, or the study is otherwise released from coverage of the federal regulations, the Investigator shall promptly notify the Chairperson and shall provide documentation indicating such release to the satisfaction of the Chairperson. At the conclusion of any study or upon FDA or HHS release, the IRB may require follow-up information and documentation of a completed or discontinued study as it may determine appropriate.

V. INFORMED CONSENT

A. GENERAL. One of the most fundamental conditions for the conduct of research involving human subjects is the condition that all subjects participate voluntarily after giving truly informed consent. Obtaining informed consent is, first and foremost, the Investigator's responsibility. Lack of informed consent may expose the Investigator to a claim of medical malpractice (and in some settings, a claim of assault or battery). The IRB is also charged with oversight responsibility for the informed consent process, which is exercised by (i) approving the ICF and other informed consent documents to be used, (ii) obtaining the Investigator's certification that informed consent will be obtained and documented, and (iii) reserving the right to audit the consent process and documentation. The FDA Regulations and Common Rule set forth requirements for the informed consent process and elements that must be in the ICF. The ICF and other consent documents shall meet the all regulatory requirements regardless of funding, sponsorship, and topic to be researched. Throughout this Handbook, the term "Subject" shall be deemed to include the Subject or the Subject's legally authorized representative as determined by applicable NMHS policies and procedures.

B. THE PROCESS OF INFORMED CONSENT

1. Obtaining Consent, Understandability. The Investigator has a legal and an ethical obligation to ensure prospective Subjects have sufficient knowledge and comprehension of the elements of informed consent. This means prospective subjects must be able to make an informed decision to participate in research. Informed consent shall be documented with a complete ICF written in clear, understandable language at an appropriate reading level as further explained below. Informed consent may be obtained by the Investigator, research nurse or other qualified professional as determined by the Investigator and the Sponsor.

2. Responsibility. The ICF does not, alone, constitute informed consent. Rather, the ICF should serve as a guide by which the person facilitating the informed consent process defined above obtains informed consent with the prospective Subject. During the process of informed consent, each element of consent detailed below shall be carefully, patiently and simply explained to the prospective Subject. In addition, the person facilitating informed consent should periodically assess the prospective Subject's comprehension by asking appropriate questions. In some cases, the consent process should be extended over several days and involve other individuals, such as the prospective Subject's spouse, family, other healthcare professionals or other ancillary personnel. Although the Investigator may not be the person facilitating the informed consent process with prospective Subjects, the Investigator bears full and ultimate responsibility for obtaining valid informed consent from the Subject.

3. Explanation of Subject Rights. During the informed consent process, the person facilitating the informed consent process, as outlined above, shall explain to the Subject their rights as a research participant. The explanation of a research Subject's rights is considered part of the informed consent process and serves to demonstrate a commitment to the conduct of human subject research with the highest integrity and skill possible. The person facilitating the informed consent process shall carefully explain to the Subject that the Protocol is a research Protocol, potentially involving experimental treatment; there may be no intention or assurance of therapeutic benefit to the Subject, understanding that prospective Subjects may overestimate the potential benefit unless clearly told otherwise; and the Subject has a choice to consent or not consent. It should also be made clear that the choice to enroll will not impact the Subject's care with NMHS.

C. DOCUMENTATION OF INFORMED CONSENT

1. Determination and Documentation of Informed Consent. After the person facilitating the informed consent process, as outlined above, has determined that the prospective Subject has sufficient knowledge and comprehension of each element of consent within the ICF, the Subject should read (or have read to the Subject) and voluntarily sign and date the ICF. The Investigator or authorized staff shall also sign and date the ICF. Authorized staff may sign an ICF for a given study only if they possess sufficient information about the study and are authorized by the Investigator to obtain informed consent.

2. Mode of Delivery. To the greatest extent possible, the informed consent process should be conducted in person and not remotely (such as telephone or video). However, when geographic distances between the Subject and the research site are significant or a face-to-face discussion cannot reasonably be arranged or should not be arranged due to the individual circumstances of the Subject, conducting the process remotely may be considered and determined by the Principal Investigator. Use of remote consent is always subject to the requirement that the consent process must be understandable and meaningful to the Subject and must result in true informed consent. Some Subjects may have language, speech, hearing or other communication issues that make telephone or video consent impossible. Other technologies may be used to enhance the telephone or video consent process when available.

   When telephone or video consent is used, written consent may be obtained using a mailed, faxed, or scanned and e-mailed ICF. In such cases, the Subject should be sent a copy of the entire ICF prior to the telephone or video discussion so the Subject has the opportunity to review it in advance. Following the remote informed consent discussion, the Subject should sign and return the consent document to the Investigator or study team member at the research site via mail, fax, or email. In the rare instance that written consent cannot be obtained, applicable NMHS policies and procedures shall be followed with respect to verbal consent.

3. Witnesses. If required by the Sponsor, NMHS, or the Principal Investigator, the informed consent process and signature must be witnessed and the ICF shall be signed by such witness ("Witness"). In such a case, the Witness must be present during the entire presentation of the ICF and other informed consent documents and shall sign the ICF after the Subject has signed, so as to verify the entire consent document was read by the Subject and the ICF was signed as a voluntary act.

4. Capacity of Subject. If a Subject does not appear to have sufficient capacity to comprehend the disclosures or appreciate the effect of their actions, an Investigator shall be consulted on how to address the informed consent process. Deference shall be given to the Investigator's clinical determination of capacity, and applicable NMHS policies and procedures related to capacity shall be followed. If permitted by the Investigator and such policies and procedures, the person facilitating the informed consent process may obtain consent from a legally authorized representative rather than the Subject. Legal counsel may be consulted to determine who may act as a legally authorized representative for an incapacitated Subject.

5. Copy to Subject. A copy of the signed ICF and any other applicable informed consent document shall be given to the Subject.

D. INFORMED CONSENT FORM

1. Identification. The ICF should clearly identify itself as an informed consent form for a research study. Once Approved by the IRB, the ICF shall identify such fact, include the Approval date(s), and identify the Study Sponsor. The individual being asked to participate should be referred to as the "Subject" in the ICF.

2. Style. It is recommended that the ICF be written in the second person throughout (e.g., you are invited to participate, you will be assigned, etc.). Use of the second person better communicates that the choice to participate is made by the prospective Subject.

3. Readability. Generally, the ICF should be written at a reading level not exceeding sixth (6th) to eighth (8^{th}) grade. However, all facts and circumstances shall be taken into account in determining whether an ICF is written in an understandable and appropriate manner given the prospective Subjects. Headings and subheadings should be used to increase readability and comprehension. Terms that are commonly used by members of a profession, such as the medical profession, shall be defined and sufficiently explained. If there is any doubt that a term may not be understood, a simpler term should be used or a definition should be added.

4. Exculpatory Language. The ICF shall not contain any exculpatory language through which the Subject waives or appear to waives any of the Subject's legal rights or releases the Investigator, the Sponsor, or NMH or its agents from legal liability.

5. Foreign Language Consent Documents. The ICF shall be translated and presented via a qualified interpreter, in accordance with applicable NMHS policies and procedures, in a language in which a Subject is fluent. The Investigator shall arrange for translations or interpreters to assist non-English speaking Subjects with the informed consent process.

E. ELEMENTS OF INFORMED CONSENT.

The FDA Regulations and the Common Rule have different requirements for what must be in the ICF.

1. FDA Regulations (21 CFR Parts 50, 56, 312, 812). Research governed by the FDA Regulations generally consists of research of foods, dietary supplements, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products (21 CFR 50.1). Research governed by the FDA Regulations shall have an ICF containing all of the following:

   a. Complete title of the study. The complete official title of the study should be stated. It is important for Subjects to be aware of the title of the study even if it is highly scientific. In order to facilitate maintenance of records, the same title should be used on the IRB application, Protocol, and ICF.

   b. Invitation for the Subject to participate in research. The ICF shall contain a clear invitation to participate in a research study. The term "experimental" may be used and is encouraged. The ICF should instruct the Subject to be sure to ask questions and fully understand the information set forth, before deciding whether to volunteer for the study and sign the ICF.

   c. Statement that the study involves research.

d. Explanation of the purposes of the research. The ICF shall briefly describe why the prospective Subject is eligible to participate (e.g., inclusion criteria such as a specific disease, condition, characteristic, background). The ICF shall give the Subject a sound context in which to consider the risks, benefits, and alternatives of the study. This section should be carefully written, and should contain a clear, understandable and accurate statement of the scientific purpose and objectives of the study, which should help the Subject assess the importance of the study relative to individual values. When appropriate, this statement should include not only the immediate purpose of the study, but also any larger, ultimate purpose. If there are primary (e.g., to evaluate toxicity) and secondary (e.g., to evaluate possible benefit) purposes, they should be separately identified, clearly enough that the patient is not misled about issues of risk and benefit. The statement of purpose must not understate the experimental nature of the research, understate the purpose of determining drug toxicity or other risks, or mislead the Subject into believing that there is more therapeutic potential than known. The ICF shall include the FDA status of any study drugs or medical devices (e.g., Drug A is an investigational drug while Drug B is FDA approved for this use).

e. Expected duration of the subject's participation.

f. Description of the procedures to be followed. The ICF shall contain a description of the study design (e.g., longitudinal, single-blind, double- blind, placebo), method of Subject assignment to groups (e.g., randomization) and probability of assignment (e.g., 50-50 chance). Despite the fact that Subjects may be kept unaware of treatment assignments in blinded studies and research involving placebos, Subjects must be made aware of all the possible interventions and the method of assignment. The ICF shall contain a sequential description of each procedure to be applied to Subjects and how often it will be performed. All procedures, both experimental and non-experimental, must be disclosed and described. Procedures that are experimental and/or performed for research purposes only should be identified as such. In some research, it may be appropriate to identify the individual(s) who will perform the procedures and/or interact with the Subject. The ICF should not contain detailed instructions to the Subject that do not impact significantly on the informed consent process. Detailed instructions should be placed on a separate handout.

g. A statement of where the research will be conducted, when the research will be conducted, and how much time (per session and in total) will be required of the Subject.

h. A statement concerning any medications, therapeutic regimens, foods, or other substances that are contraindicated or disallowed either before or during participation in the study.

i. Identification of any procedures that are experimental;

j. Description of any reasonably foreseeable risks or discomforts to the subject. The ICF shall fully disclose all known or reasonably anticipated risks that the Subject would likely consider significant in deciding whether or not to participate in the research. The concept of risk includes discomfort, burden, or

inconvenience a Subject may experience as a result of the research procedures. The ICF shall contain immediate and latent risks of each procedure or intervention carried out for research purposes. In therapeutic research it is often advantageous to also disclose the risks of procedures carried out solely for therapeutic purposes. Each procedure or intervention should be identified and then the associated risks described (e.g., aspirin: dizziness, ringing in the ears, bleeding inside the stomach, etc.). Risks should not be understated or overstated. In some cases it is considered desirable to cite statistical probability of risk occurrence, risk prevention measures, reversibility, and treatment, but this should be done very cautiously since any statistical values or other qualifiers (e.g., "likely," "rare") must be current when used and then must be updated if and when they change. The terms "minimal risk," "greater than minimal risk" and "significant risk" generally should not be used in the consent document. A Subject is not likely to understand the meaning of these terms. In most therapeutic research projects the consent document should also state that there may be risks associated with the research that are currently unknown.

k. Description of any benefits to the subject or to others that may reasonably be expected from the research. The ICF shall state whether there are any direct benefits to the Subject or to others that may reasonably be expected as a result of participation in the study. Examples of direct benefits to the Subject include treatment of an illness, or knowledge of value to the Subject (e.g., results of tests). The potential benefits to the Subject must not be overstated, coercive, or guaranteed. If there are no benefits to the Subject, this should be stated and should be explained before the Subject's consent is accepted. Financial remuneration for a Subject's participation shall not be included in this section of the ICF. Instead, all forms of compensation shall be disclosed in a separate section of the ICF.

l. Disclosure of appropriate alternative procedures or courses of treatment, if any, that may be available to the Subject. The ICF shall state in reasonable detail any known therapeutic alternatives available to the Subject in the non-research and/or research context which may be of reasonable benefit to the Subject. When appropriate, the relative risks and benefits of the therapeutic alternative versus the study should be stated. In some cases it may be appropriate to state the option of no treatment or hospice/comfort care.

m. Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. The ICF shall state that any information obtained in connection with the study and which could identify the Subject will remain confidential and will be disclosed only with the Subject's HIPAA Authorization. However, the Subject shall be advised that information regarding the Subject may be sent to or accessed by representatives of the Investigators, NMH, the IRB, and the Sponsor (identified by name). The ICF shall advise that information from the study may be published in scientific journals or presented at scientific meetings but the Subject's identity will be kept strictly confidential.

n. Statement that notes the possibility that the FDA or HHS may inspect the records that identify the Subject.

o. For research involving more than minimal risk, an explanation as to: (i) whether any compensation is available if injury occurs; and (ii) whether any medical treatments are available if injury occurs, and if so, what they consist of or where further information may be obtained.

p. Explanation of whom to contact for answers to pertinent questions about the research and research Subject's rights, and whom to contact in the event for a research-related injury. The ICF shall advise the Subject, in simple terms, what to do in case of an emergency or research-related injury.

q. Statement that participation is voluntary, refusal to participate will involve no penalty or less of benefits to which the Subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the Subject is otherwise entitled.

r. Statement that the particular treatment or procedure may involve risk to the Subject or embryo or fetus that may be unforeseeable.

s. Circumstances under which the Subject's participation may be terminated by the investigator without regard to the Subject's consent.

t. Any additional costs to the Subject that may result from participation in research. This ICF shall state as clearly as possible, all financial obligations of the Subject with respect to participation in the study (e.g., financial responsibility for physician fees, hospital charges, medications, pharmacy charges, laboratory tests, post-treatment follow-up). If there is potential for additional cost to the Subject as a consequence of procedures carried out for research purposes (e.g., extended hospitalization, additional tests), this should be disclosed. The document should disclose that certain costs may not be covered by insurance or other third-party payer. If the Sponsor or another source is providing something that is free to Subjects, this should be stated with care to ensure that the Subject is not misled into believing that other costs (e.g., physician and hospital care) will be covered. The ICF shall clearly delineate the costs covered by the Sponsor and those that will be billed to the Subject's insurer and may become the financial responsibility of the Subject, if denied.

u. Consequences of a Subject's decision to withdraw from research and procedures for orderly termination of participation by the Subject.

v. Statement that significant new findings developed during the course of research that may relate to the Subject's willingness to continue participation will be provided to the Subject.

w. Any compensation or other remuneration to be paid or provided to Subjects. The ICF shall state any compensation for participation in research. Cash payments should be stated in dollar amounts and any conditions such as partial payment or no payment for early termination and bonuses for completion should be stated. The nature, amount and method of payment of financial or other compensation must not constitute undue inducement of the Subject (e.g., the compensation alone should not serve as sufficient inducement for the Subject to volunteer). If

no compensation or remuneration will be paid or provided, this shall be stated in the ICF.

x. Approximate number of Subjects involved in the study.

y. Whether an Investigator is receiving any direct compensation or remuneration. The ICF shall advise the Subject if the Investigator has a financial interest in the study, and explain such interest in reasonable detail.

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

2. The Common Rule (45 CFR Part 46). Research governed by the Common Rule generally consists of all research not otherwise governed by the FDA Regulations. Research governed by the Common Rule shall have an ICF containing all of the following:

a. Complete title of the study. The complete official title of the research study should be stated. It is important for Subjects to be aware of the title of the research study even if it is highly scientific. In order to facilitate maintenance of records, the same title should be used on the IRB application, Protocol and the ICF.

b. At the beginning of the ICF: A concise and focused presentation of the key information (including why one may/may not want to participate).

c. Statement that the study involves research (46.116)(b)(1).

d. Explanation of the purposes of the research. The ICF shall briefly describe why the prospective Subject is eligible to participate (e.g., inclusion criteria such as a specific disease, condition, characteristic, background). The ICF shall give the Subject a sound context in which to consider the risks, benefits, and alternatives of the study. This section should be carefully written, and should contain a clear, understandable and accurate statement of the scientific purpose and objectives of the research, which should help the Subject assess the importance of the study relative to individual values. When appropriate, this statement should include not only the immediate purpose of the study, but also any larger, ultimate purpose. If there are primary (e.g., to evaluate toxicity) and secondary (e.g., to evaluate possible benefit) purposes, they should be separately identified, clearly enough that the patient is not misled about issues of risk and benefit. The statement of purpose must not understate the experimental nature of the research, understate the purpose of determining drug toxicity or other risks, or mislead the Subject into believing that there is more therapeutic potential than known.

e. Expected duration of the study.

f. Description of procedures to be followed. The ICF shall contain a description of the study design (e.g., longitudinal, single-blind, double- blind, placebo), method

of Subject assignment to groups (e.g., randomization) and probability of assignment (e.g., 50-50 chance). Despite the fact that Subjects may be kept unaware of treatment assignments in blinded studies and research involving placebos, Subjects must be made aware of all the possible interventions and the method of assignment. The ICF shall contain a sequential description of each procedure to be applied to Subjects and how often it will be performed. All procedures, both experimental and non-experimental, must be disclosed and described. Procedures that are experimental and/or performed for research purposes only should be identified as such. In some research, it may be appropriate to identify the individual(s) who will perform the procedures and/or interact with the Subject. The ICF should not contain detailed instructions to the Subject that do not impact significantly on the informed consent process. Detailed instructions should be placed on a separate handout.

g. The ICF shall contain a statement of where the research will be conducted, when the research will be conducted, and how much time (per session and in total) will be required of the Subject.

h. The ICF shall contain a statement concerning any medications, therapeutic regimens, foods, or other substances that are contraindicated or disallowed either before or during participation in the study.

i. Identification of any procedures that are experimental.

j. Description of any reasonably foreseeable risks or discomforts to the subject. The ICF shall fully disclose all known or reasonably anticipated risks that the Subject would likely consider significant in deciding whether or not to participate in the research. The concept of risk includes discomfort, burden, or inconvenience a Subject may experience as a result of the research procedures. The ICF shall contain immediate and latent risks of each procedure or intervention carried out for research purposes. In therapeutic research it is often advantageous to also disclose the risks of procedures carried out solely for therapeutic purposes. Each procedure or intervention should be identified and then the associated risks described (e.g., aspirin: dizziness, ringing in the ears, bleeding inside the stomach, etc.). Risks should not be understated or overstated. In some cases it is considered desirable to cite statistical probability of risk occurrence, risk prevention measures, reversibility, and treatment, but this should be done very cautiously since any statistical values or other qualifiers (e.g., “likely,” “rare”) must be current when used and then must be updated if and when they change. The terms “minimal risk,” “greater than minimal risk,” and “significant risk” generally should not be used in the consent document. A Subject is not likely to understand the meaning of these terms. In most therapeutic research projects, the consent document should also state that there may be risks associated with the research that are currently unknown.

k. Description of any benefits to the subject or to others that may be reasonably expected from the research. The ICF shall state whether there are any direct benefits to the Subject or to others that may reasonably be expected as a result of participation in the study. Examples of direct benefits to the Subject include treatment of an illness, or knowledge of value to the Subject (e.g., results of

tests). The potential benefits to the Subject must not be overstated, coercive, or guaranteed. If there are no benefits to the Subject, which is usually the case in non- therapeutic research, this should be stated and should be explained orally before the Subject's consent is accepted. Financial remuneration for a Subject's participation shall not be included in this section of the ICF. Instead, all forms of compensation shall be disclosed in a separate section of the ICF.

l. Disclosure of alternative procedures or courses of treatment, if any, that might be advantageous to the subject. The ICF shall state in reasonable detail any known therapeutic alternatives available to the Subject in the non-research and/or research context that may be of reasonable benefit to the Subject. When appropriate, the relative risks and benefits of the therapeutic alternative versus the research should be stated. In some cases (e.g., terminally ill patients) it may be appropriate to state the option of no treatment or hospice/comfort care.

m. Statement describing the extent, if any, to which confidentiality of records identifying subjects will be maintained.

n. 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 whether further information may be obtained.

o. Explanation of whom to contact for answers to pertinent questions about the research and research subjects rights.

p. Whom to contact for research-related injuries. The ICF shall advise the Subject, in simple terms, what to do in case of an emergency or research-related injury.

q. Statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the Subject is otherwise entitled.

r. Statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the Subject is otherwise entitled.

s. If research involves collection of identifiable private information or identifiable biospecimens.

t. Statement that identifiers may be removed from identifiable private information or identifiable biospecimens and that information or biospecimens could be used for future research studies or distributed to another investigator for future research without additional informed consent, or a statement that information or biospecimens, even if identifiers are removed, will not be used or distributed for future research studies.

u. Statement that the particular treatment or procedure may involve risks to the Subjects, embryo or fetus that may be unforeseeable.

v. Anticipated circumstances under which the Subjects participation may be terminated by the investigator without regard to the Subjects consent;

w. Additional costs to the subject that may result from participation in the research. This ICF shall state as clearly as possible, all financial obligations of the Subject with respect to participation in the study (e.g., financial responsibility for physician fees, hospital charges, medications, pharmacy charges, laboratory tests, post-treatment follow-up). If there is the potential of additional cost to the Subject as a consequence of procedures carried out for research purposes (e.g., extended hospitalization, additional tests), this should be disclosed. The document should disclose that these costs may not (or probably will not) be covered by insurance or other third-party payor. If the Sponsor or another source is providing something that is free to Subjects, this should be stated with care to ensure that the Subject is not misled into believing that other costs (e.g., physician and hospital care) will be covered. The ICF shall clearly delineate the costs covered by the Sponsor and those that will be billed to the Subject's insurer and may become the financial responsibility of the Subject, if denied.

x. Any compensation or other remuneration to be provided to Subjects. The ICF shall state any compensation for participation in research. Cash payments should be stated in dollar amounts and any conditions such as partial payment or no payment for early termination and bonuses for completion should be stated. The nature, amount, and method of payment of financial or other compensation must not constitute undue inducement of the Subject (e.g., the compensation alone should not serve as sufficient inducement for the Subject to volunteer). When establishing the amount and type of compensation, the Investigator should consider the background and socioeconomic status of the Subject population. If no compensation or remuneration will be paid or provided, this shall be stated in the ICF.

y. Consequences of a Subjects decision to withdraw from the research.

z. Procedures for orderly termination of participation by the Subjects.

aa. Statement that significant new findings developed during the course of the research that may relate to the Subject’s willingness to continue will be provided to the subjects.

bb. Approximate number of Subjects involved in the study.

cc. If applicable, a statement that the Subjects biospecimens, even with removed identifiers, may be used for commercial profit and whether the Subject will or will not share in this commercial profit;

dd. Statement regarding whether clinically relevant research results, including individual research results, will be disclosed to Subjects, and if so, under what conditions;

ee. For research involving biospecimens, whether the research will or might, if known, include whole genome sequencing.

F. CONSENT/ASSENT PROCEDURES FOR RESEARCH SUBJECTS WHO ARE MINORS

1. Defined. The term "Minor" means: a person under the age of 19 years in Nebraska or under the age of 18 in Iowa, who is not emancipated. The IRB shall rely on applicable NMHS policies and procedures to determine the status of emancipation.

2. Capacity of Minor. Generally, Minors lack legal capacity to consent on their own behalf. Attempts shall be made to solicit the consent of each parent of a Minor Subject. However, the consent of both parents is not necessary unless otherwise set forth herein. A parent or legal guardian must give consent on behalf of the Minor and sign the ICF. Minors are not permitted to provide consent to participate in research unless one of the following exceptions applies:

a. If the Minor has been given written permission by a parent/legal guardian, the Minor may then consent to participate in research.

b. Minors who are married may consent to participate in research.

c. Minors who are active military status are considered emancipated and they may consent to participate in research.

d. A parent who is a Minor may consent to participate in research for the Minor's child.

3. State Law and Other Applicable Law. A Minor may, with IRB approval, legally consent on the Minor's own behalf if such consent is permissible under applicable law (e.g., use of contraceptives or treatment of venereal disease).

4. Minor with Divorced Parents. Generally, either parent may consent to participate in research on behalf of their own Minor child, unless the parent's parental rights have been terminated or a Court Order specifies otherwise.

5. Greater than Minimal Risk. In cases where the research involves a greater than minimal risk to the child and no prospect of direct benefit to the Minor, yet is likely to yield generalizable knowledge about the Subject's disorder or condition, consent of both parents must be obtained. However, this rule does not apply when one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has the legal responsibility for the care and custody of the Minor.

6. Assent from the Minor. In addition to obtaining the parent's/legal guardian's consent, the Investigator must also solicit assent of a Minor age 7 and older, unless the Minor displays intellectual or emotional development below that of the average 7-year-old child. Obtaining assent shows respect for a Minor's developing autonomy. In most circumstances, a child's deliberate objection should be regarded as a veto to the child's involvement in research. However, parents/legal guardians may, with IRB (via Approval) and Investigator approval, override a child's objections to interventions that hold the prospect of direct benefit to the child.

7. Changes to Law. The law related to informed consent of Minors frequently changes. Thus, NMHS policy(ies) on informed consent of Minors shall be followed in conjunction with this Subsection E, and in the event of conflict, such policy(ies) shall control.

G. CONSENT TO USE TISSUE OR RECORDS FOLLOWING DEATH

Research Subjects will sometimes give informed consent and HIPAA Authorization to use their blood, tissue, other samples and/or records for current or future research, either as their sole means of

participating in a study or ancillary to a therapeutic study in which they are participating. This includes but is not limited to Secondary Site Studies where the only activity at NMH is the transmittal of blood, tissue, other samples or records to the research institution. Unless (i) the informed consent or HIPAA Authorization expressly states that it expires upon death, (ii) an event of expiration listed in the ICF or HIPAA Authorization occurs (e.g., the end of the research study), or (iii) the Subject's legally authorized representative expressly revokes the ICF or HIPAA Authorization; the ICF/HIPAA Authorization shall survive death and the use of the Subject's blood, tissue, other samples or records may continue following death without further consent.

All requests for access to stored tissue for research purposes require Approval by the IRB. The applicable NMHS policy(ies) on tissue donation shall be followed, and in the event of conflict between this Handbook and such policy(ies), the policy(ies) shall control.

H. AUTHORIZATION FOR USE AND DISCLOSURE OF INFORMATION

1. General. The Health Insurance Portability and Accountability Act of 1996 ("HIPAA") governs the use and disclosure of Subjects' health information, often referred to as Protected Health Information ("PHI"), and sets standards for the privacy rights of Subjects to ensure Subjects understand and control how their PHI is used. Under HIPAA, an Affiliate may use or disclose PHI for research, regardless of funding of the research, provided one of the following is met:

a. The Subject provides authorization to use or disclose their PHI (referred to herein as a "HIPAA Authorization").

b. The Affiliate obtains documentation that an alteration to or waiver of the requirement to obtain Authorization to use or disclose PHI from the Subject is granted by the MH IRB or an external IRB, as permitted by the Chairperson.

c. The Affiliate obtains from the Investigator representations that:

   i. The use or disclosure is sought solely to review PHI as necessary to prepare a research Protocol or for similar preparatory purposes;

   ii. No PHI is to be removed from the Affiliate by the Investigator in the course of their review; and

   iii. The PHI is necessary for research purposes.

d. The Affiliate obtains from the Investigator:

   i. Representation that the use or disclosure is solely for research on the PHI of decedents;

   ii. Documentation of the death of such individual, if requested; and

   iii. Representation that the PHI is necessary for research purposes.

2. Waiver or Alteration of HIPAA Authorization. The IRB may, via Approval, waive, or alter the requirement to obtain a HIPAA Authorization if:

a. The use or disclosure of PHI involves no more than a minimal risk to the privacy of Subjects, based on, at least, the presence of the following elements:

i. An adequate plan to protect the identifiers from improper use and disclosure;

ii. 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 for retaining the identifiers or such retention is otherwise required by law; and

iii. Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research, or for other research for which the use or disclosure of PHI would be permitted by HIPAA.

b. The research could not practicably be conducted without the waiver or alteration; and

c. The research could not practicably be conducted without access to the use of the PHI.

3. Documentation of Waiver or Alteration. If the requirement to obtain HIPAA Authorization to use or disclose PHI from a Subject is altered or waived, documentation must include all of the following:

a. Statement identifying the IRB and the date on which the alteration or waiver was Approved;

b. A statement that the IRB has determined that the alteration or waiver of HIPAA Authorization, in whole or part, satisfies the criteria above required for waiver or alteration;

c. A brief description of the PHI for which use or access has been determined to be necessary by the IRB;

d. A statement that the alteration of waiver has been reviewed and Approved under either normal or Expedited Review; and

e. The documentation of the alteration or waiver must be signed by the Chairperson or other member as designated by the Chairperson.

4. Other Conditions of HIPAA Authorization.

a. A HIPAA Authorization may be combined with any other type of written permission or consent for the same or another research study.

b. It is permissible to condition the provision of research-related treatment on the signing of a HIPAA Authorization.

c. A valid HIPAA Authorization requires an expiration date. The statement “end of the research study,” “none,” or similar language is sufficient in the context of research.

5. Limited Data Set. An Affiliate may use or disclose a Limited Data Set for research purposes as permitted by HIPAA. A Limited Data Set is PHI that excludes 16 direct identifiers of the Subject.

VI. INVESTIGATOR RESPONSIBILITIES, STANDARDS AND CORRECTIVE ACTION

A. RESPONSIBILITIES AND STANDARDS.

Investigators participating in research studies under the IRB are each independently responsible for meeting and keeping current the standards set forth in this Handbook during their time as Investigator of any study, whether it constitutes Research/Clinical Investigation under applicable law or not. Failure to meet these standards could result in Disapproval, Conditional Approval, or Tabling of a study, or other sanctions as determined by the Chairperson or the IRB. The IRB Manager will monitor Investigator's compliance under these standards and report deficiencies to the Chairperson.

B. CREDENTIALS

1. Investigators shall:

    a. Be specifically approved by the IRB to participate as a Principal Investigator or Secondary Investigator.

    b. Be a member of the Medical Staff at the Affiliate in which the research is to be performed.

    c. Maintain clinical privileges as necessary to participate in the study at such Affiliate.

    d. Maintain credentials, licensure and other training required by the Sponsor of the study in which the Investigator will be acting in such capacity.

    e. Notify the applicable Medical Staff office of any significant changes in the Investigator's licensure, training or experience as related to the research study, authorization from the Sponsor or other change in the relationship with the Sponsor, and any adverse actions by the DHHS and/or the FDA.

C. IRB–RELATED TRAINING

1. Investigators shall:

    a. Review, understand and abide by the terms of this Handbook.

    b. Complete Investigator training courses or other courses as Approved and required by the IRB. Investigators shall provide documentation of successful completion of such training to the IRB Manager prior to the Investigator's submission of their first New Study Application. The costs of registration may be paid by an Affiliate of NMHS. Investigators who have completed IRB training at a different institution can, at the Chairperson’s option, satisfy the IRB’s training requirement by providing documentation of successful completion to the IRB Manager.

    c. Every three (3) years following completion of the initial required IRB training, Investigators shall complete a supplemental training course as required by the IRB and provide documentation of successful completion to the IRB Manager. Exceptions may be permitted by the Chairperson.

    d. Cooperate with and complete any other reasonable request by the IRB for continued education.

D. PAPERWORK, REPORTING

1. Investigators shall:

   a. File all reports, including Status Reports, Study Closure Forms, Adverse Event Forms, Protocol Deviation Report Forms, and Miscellaneous Report Forms, as required by the Common Rule or FDA Regulations, with the IRB on a timely and complete basis.

   b. Complete, on a timely basis, all reports required by the applicable Sponsor, the FDA, or other regulating authorities.

   c. Immediately notify the IRB Manager, of any temporary or permanent suspension or closure of a study in which the Investigator is participating; any changes in the Investigator's authority to participate in the study; or any pending or completed actions to suspend or terminate the Investigator's authority to participate in government-sponsored research programs, government grants, government contracts, or human subject research.

   d. Obtain prior approval from the IRB for any Modifications except those necessary to eliminate apparent immediate hazards to Subjects.

   e. Provide the IRB with prompt reports of any unanticipated problems involving risks to Subjects or others as set forth in this Handbook.

   f. Provide the IRB with prompt reports of serious or continuing noncompliance with the Common Rule, FDA Regulations or other applicable laws, or the requirements or determinations of the IRB.

E. INFORMED CONSENT

1. Investigators shall:

   a. Unless waived, obtain full informed consent from each Subject participating in a study, utilizing the respective IRB-Approved ICF for such study.

   b. Notify Subjects of any material new information that may affect the Subject's willingness to participate in the study.

   c. Keep copies of all signed ICF’s and other study- related documents on file for the entire duration of the study, and for the time period required by Applicable NMHS policies and procedures.

   d. Provide current copies of the ICF being used, and certify that informed consent is being obtained and retained in all cases, as part of the process of annual reporting to the IRB.

F. FINANCIAL INTERESTS

1. Investigators shall:

   a. Assure no financial interest exists that may influence the Investigator’s decision to enroll a patient as a study Subject, or influence study procedures or outcomes.

b. Fully disclose to the IRB, on the New Study Application or, if after submission of the New Study Application, in written form to the IRB Manager, and subsequent Status Reports:

i. All direct or indirect payments from the Sponsor or other Sponsor-related sources to the Investigator participating in the Sponsor's research; and

ii. Any Reportable Financial Interest the Investigator has in the study.

The IRB has established the following definition, modeled after the FDA's definition of the same:

"Reportable Financial Interest" means any interest of the Investigator or the Investigator's spouse or children, or of any Sponsor-related entity (including foundation, corporation, LLC, partnership, or other entity related to the Sponsor) in which the Investigator or the Investigator's spouse or children:

i. Has Received any compensation by any Sponsor of the study in which the value of compensation could be affected by study outcome.

ii. Has a proprietary interest in a Sponsor's tested product including, but not limited to, a patent, trademark, copyright, or licensing agreement.

iii. Has any equity interest in any Sponsor of the study, i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices. The requirement applies to interests held during the time the Investigator is carrying out the study and for one year following completion of the study.

iv. Has any equity interest in any Sponsor of the study if the Sponsor is a publicly held company and the interest exceeds $50,000 in value. The requirement applies to interests held during the time the Investigator is carrying out the study and for one year following completion of the study.

v. Has received significant payments of other sorts ("SPOOS"). SPOOS are payments that have a cumulative monetary value of $25,000 or more and are made by any sponsor of the study to the Investigator or the Investigator's institution during the time the Investigator is carrying out the study and for one year following completion of the study. This would include payments that support activities of the Investigator (e.g., a grant to the Investigator or to the institution to fund the Investigator's ongoing research or compensation in the form of equipment), exclusive of the costs of conducting the study or other clinical studies, or to provide other reimbursements such as retainers for ongoing consultation or honoraria.

vi. Owns five percent (5%) or more of the voting or non-voting shares or interests;

vii. Is a trustee, a director, a manager, or a compensated employee of such entity;

viii. Receives consulting fees, honoraria, gifts, or other emoluments, or "in kind" compensation, directly or indirectly from the Sponsor or another person or entity, or for any other purpose not directly related to the reasonable costs of conducting the research, that in the aggregate have exceeded or are expected to exceed $10,000 in any twelve-month period;

ix. Has equity interests, including stock options, of any amount in the Sponsor or any Sponsor-related entity, provided that equity interests of less than 5% in a publicly traded company, or of any amount in a publicly traded diversified mutual fund, are excluded;

x. Receives royalty income or the right to receive future royalties under a patent, license or copyright, where the study is directly related to the licensed technology or work;

xi. Receives any non-royalty payments or entitlements to payments in connection with the study that are not directly related to the reasonable costs of the study. This includes any bonus or milestone payments to the Investigators in excess of reasonable costs incurred;

xii. Serves as an officer, director or in any other managerial or fiduciary role for the Sponsor, whether or not remuneration is received for such service.

Written, pre-determined payments that are directly related to reasonable costs incurred in the conduct of a study are excluded from the definition of Reportable Financial Interest.

c. Cooperate with any directive of the IRB to address Reportable Financial Interests. The IRB may, in its discretion, request additional information at any time related to a Reportable Financial Interest. The IRB may, via Approval, conclude that under the circumstances, the Reportable Financial Interest does or does not pose any additional risk to the welfare of the Subjects or the integrity of the research.

d. Disapprove or Approve a study despite the existence of a Reportable Financial Interest.

e. Impose periodic monitoring and reporting requirements as a condition of Approval.

f. Require disclosure of the Reportable Financial Interest in the ICF.

g. Take other action as deemed reasonably appropriate by the IRB.

h. Not accept payments, from the Sponsor or otherwise, which are conditioned upon a particular research result or are tied to successful research outcomes.

i. Not accept payments for Subject enrollment or for referral of Subjects to the study, unless such payments are reasonably related to actual costs incurred and are compliance with applicable federal and state laws and regulations governing referrals and kickbacks.

j. Assure charges for products and services rendered in the course of the research study are proper, confirming that (i) charges to the Subject are consistent with the representations made during the informed consent process and contained in the ICF, (ii) charges to Medicare, Medicaid or insurers are limited to permitted/non-excluded charges, and (iii)

charges are not duplicate-billed to the Subject and a third-party payor or to multiple third-party payers or grant agencies.

G. AUDITS AND INVESTIGATIONS. Investigators shall:

a. Cooperate fully, at all times upon request of the IRB, in any audits or investigations by or on behalf of the IRB.

b. Cooperate fully in any audits or investigations by the Sponsor, the FDA, HHS or any regulatory body and notify the IRB promptly in the event any such audit or investigation is initiated.

H. INVESTIGATOR AGREEMENT

Investigators shall execute and return to the IRB Manager, prior to the submission of a New Study Application or an Investigator's participation in a study, an Investigator Agreement.

I. CORRECTIVE ACTION

By participating as an Investigator in a study performed at an Affiliate, the Investigator accepts and agrees to abide by all of the terms set forth in this IRB Handbook, as well as all comply with all applicable laws and regulations and Sponsor requirements. In the event an Investigator fails to do so, the IRB shall have the authority, via Approval, and the responsibility, to take any corrective action as deemed reasonably appropriate to the circumstances. The IRB will generally adhere to the following principles:

1. Delinquent Reports. Failure to timely and completely submit the reports specified in this Handbook or other IRB-required reports to the IRB, or failure to respond on a timely and complete basis to the IRB's request for information, may result in the IRB suspending all study-related activity. Continued non-compliance may result in revocation of authority to participate as an Investigator in the study.

2. Other Violations. All other violations of the terms in this IRB Handbook or applicable laws and regulations may result in a range of corrective action depending on the facts and circumstances. Corrective action may include, but is not limited to, any of the following:

a. Suspension of the Investigator's authority to participate in the study. This may be most appropriate, for example, in the case of a failure to submit required information, temporary suspension of medical staff privileges, temporary disability, unresolved problems in the Investigator-Sponsor relationship, or other circumstances which appear amenable to correction in the foreseeable future. The IRB may choose, via Approval, to suspend the entire study or, if there are other Investigators who can properly manage the study and are not subject to the same corrective action, the IRB may via Approval, to recommend an alternate Investigator subject to the Sponsor's approval.

b. Imposition of additional reporting or monitoring requirements. This may be most appropriate, for example, in the case of an Investigator coming off suspension; or other violations where the Investigator has provided reasonable assurances of corrective measures and the IRB determines that a period of additional reporting or monitoring is warranted. Monitoring may include, but is not limited to,

additional reporting by the Investigator, on-site audits of the Investigator's research records, or auditing of the informed consent process.

c. Revocation of the Investigator's authority to participate in the research study and/or future studies at any Affiliate. This may be most appropriate, for example, in the case of continuing problems which are not resolved through dialogue and cooperation; or serious violations such as failure to obtain proper informed consent, failure to report Adverse Events, Unanticipated Problems, protocol violations, Reportable Financial Interest that are not approved by the IRB, or other violations which jeopardize Subject rights, health, or welfare.

d. In serious cases jeopardizing patient safety, the IRB may also communicate its concerns to the President of NMH, Medical Staff Executive Committee or other interested authorities. The Sponsor, DHHS, and FDA may be notified of corrective action as appropriate or as required.

3. Procedures. The IRB may act as a whole, via Approval, or delegate possible corrective action to a committee appointed by the Chairperson. The Chairperson shall have the authority to take corrective action on their own initiative between IRB meetings, when it is deemed appropriate in the best interest of study Subjects. NMH administration and legal counsel may be involved in any case as necessary. In every case, reasonable efforts will be made to talk with the Investigator and identify mutually satisfactory solutions before corrective action is imposed by the IRB.

4. Appeals. Appeals of corrective action imposed by the IRB may be requested in writing; the IRB, via Approval shall have sole discretion to determine whether or not to entertain an appeal and, if so, by what procedures.

EXHIBIT A. BELMONT REPORT

THE BELMONT REPORT
Office of the Secretary
Ethical Principles and Guidelines for the Protection of Human Subjects of Research
The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
April 18, 1979

AGENCY: Department of Health, Education, and Welfare.
ACTION: Notice of Report for Public Comment.
SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, thereby creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

National Commission for the Protection of Human Subjects of
Biomedical and Behavioral Research
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Table of Contents

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes [1] intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the wellbeing of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals [2]. By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project [3].

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. — Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of

illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

Beneficence. — Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out

much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

Justice. — Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort, **(4)** to each person according to societal contribution, and **(5)** to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. — Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a

statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject

should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest. **Voluntariness.** An agreement to participate in research constitutes a valid consent only if voluntarily given.

This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable. Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. — The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked. Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically.

This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)**Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.
3. Selection of Subjects. — Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public

funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.