NEBRASKA METHODIST COLLEGE

THE JOSIE HARPER CAMPUS

# Institutional Review Board Policy Manual

**August 2024**

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## Introduction

Research involving humans as research subjects is widely accepted as an appropriate, and in fact 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 and other researchers.

Equally accepted is the requirement that research involving human subjects must be consistent with fundamental ethical principles, including the absolute requirement that subjects participate only after truly informed, voluntary consent; and the requirements that the research follow scientifically valid protocols, that 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, the Department of Health and Human Services (HHS) all have substantial responsibilities in assuring compliance with ethical and legal standards. In addition, one body – the Institutional Review Board ("IRB") – exists solely for the purpose of protecting human research subjects through the approval, disapproval and monitoring of research studies in light of ethical standards.

## Purpose and Role of IRB

The Nebraska Methodist College Institutional Review Board (IRB) is organized and operates under the authority of the Chief Executive Officer. The IRB's purpose and role is to review and approve (or disapprove) proposed studies to ensure that:

1. Risks to subjects are minimized;

2. Risks to subjects are reasonable in relation to anticipated benefits;

3. Selection of subjects is equitable;

4. Proper informed consent will be obtained; and

5. Appropriate safeguards are maintained as necessary to assure the safety of subjects, protect privacy and protect the rights of any subjects who are likely vulnerable to coercion and undue influence due to physical or mental illness.

## NMC Statement of Principles: Mission and Core Values

**Mission**:

As a health professions institution, NMC provides educational experiences for the development of individuals in order that they may positively influence the health and well-being of the community.

**Core Values:**

**Caring**
We are concerned for the well-being of all people and demonstrate this concern through kindness, compassion and service.

**Excellence**
We expect the best from everyone and hold ourselves to the highest ideals of personal, professional and organizational performance.

**Holism**
We recognize and honor the interrelatedness of all things and all people, and are committed to the development of the whole person.

**Learning**
We embrace the experiential process by which knowledge, insight, understanding and ultimately wisdom are created for ourselves and those we serve.

**Respect**
We recognize and uphold the dignity and self-worth of every human being, and promote honest and forthright interpersonal communication and behaviors.

# Statement of Ethical Principles and Policy

## A. Ethical Principles

NMC and its IRB are guided by the ethical principles regarding 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). In addition, the requirements set forth in Title 45, Part 46 of the Code of Federal Regulations (the "Common Rule") will be met for all applicable HHS-supported research.

## B. Institutional Policy

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

1. The risks and burdens to the subjects;

2. The anticipated benefits to the subjects and others;

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

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

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

b. NMC, through its Institutional Review Board, will be responsible for the review of all research involving human subjects within the scope of the IRB's authority, including continuing review of the research.

c. NMC and all persons involved in human research will comply with federal, state or local laws governing such research.

d. NMC encourages and promotes constructive communication among the department heads, research Investigators, human 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 human subjects.

e. NMC, acting through the IRB, will conduct a quality review of the IRB Policy Manual every third year to ensure that its practices and procedures designed for the protection of the rights and welfare of human subjects are being effectively applied. The IRB may elect to review this policy manual (IRB Policy Manual) more frequently at its discretion. In addition, the IRB member credentials, CITI certifications, Annual Continuance reports, Conclusion of Study reports, continuing education, and NMC research definitions, courses, and outcomes will be reviewed annually.

f. The IRB shall consider additional safeguards in research when that research involves prisoners, pregnant women, children, individuals who are mentally disabled, other potentially vulnerable groups and human in vitro fertilization.

g. NMC and the IRB will encourage and support continuing education for IRB members and Investigators.

## Federalwide Assurance (FWA)

**FWA #: FWA00020060**

**IRB Registration #: IRB00009270**

**IORG #: IORG0007724**

It is the policy of the IRB that NMC will file and maintain an agreement with the U.S. Department of Health and Human Services' Office for Human Research Protections (OHRP) through a Federalwide Assurance FWA. NMC has declared that all institutional components listed under the NMC FWA must comply with this assurance. [45 CFR § 46.103 (a)]

NMC has determined that all human subject research will be governed by Health and Human Services regulations at 45 CFR §46 and ethical standards regardless of funding source.

NMC has determined that all of its activities related to human subject research, regardless of funding source, will be guided by the ethical principles found in the Belmont Report.

The NMC IRB does not conduct nor approve FDA regulated research.

## General Definitions

***Certification*** means the official notification by the institution (Nebraska Methodist College) to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

***Clinical Trial*** means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. ***NOTE: Nebraska Methodist College does not conduct or approve clinical trial research.***

***Department or agency head*** means the head of any federal department or agency, for example, the Secretary of HHS, and any other officer or employee of any Federal department or agency to whom authority provided by these regulations to the department or agency head has been delegated.

***Federal department or agency refers*** to a federal department or agency (the department or agency itself rather than its bureaus, offices, or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (*e.g.,* the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency.)

***Human subject*** means a living individual about whom an investigator (whether professional or student) conducting research obtains:

a. Obtains information or biospecimens through interventions or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or Obtains, uses, studies, analyzes, or generates private information or identifiable biospecimens.
b. *Intervention* includes both physical procedures by which information or biospecimens are gathered (*e.g*., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
c. *Interaction* includes communication or interpersonal contact between investigator and subject.
d. *Private information* includes information about a behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g*., a medical record).
e. *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
f. *An identifiable biospecimens* is a biospecimens for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimens.

***Institution*** means any public or private entity or agency (including federal, state, and other agencies).

***Investigator*** is the student or faculty responsible for the research study in an individual case. In sponsored studies, the Investigator has established an agreement and working relationship with the Sponsor (study organizer) before seeking IRB approval.

***IRB*** means an institutional review board established in accord with and for the purposes expressed in this policy.

***IRB approval*** means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

***IRB Manager*** is the individual employed by NMC who is charged with providing administrative support to the IRB.

***Legally authorized representative*** means an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

***Minimal risk*** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

***Public health authority*** means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

***Research*** means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. 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. Activities that meet this definition constitute research for the purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For the purposes of this part, the following activities are deemed not to be research:

a. Scholarly and journalistic activities (*e.g*., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focuses directly on the specific individuals about whom the information is collected.
b. Public health surveillance activities, including the collection and testing of information, or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associates with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or fabricated disasters).

c. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigation purposes.
d. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

***Written***, or ***in writing***, for purposes of this part, refers to writing on a tangible medium (*e.g*. paper) or in an electronic format.

# STRUCTURE AND OPERATION OF THE IRB

## IRB Scope of Authority

It is the policy of the IRB that NMC provide sufficient resources and decisional autonomy for the IRB to carry out its duties independently of NMC in full accordance with HHS policies at 45 CFR §46.

**A.** NMC through its Chief Executive Officer authorizes the IRB to independently review and approve all human subject research studies, which are conducted in whole or in part at NMC, or under the direction of any faculty, staff, student or other representative of NMC in connection with his or her institutional responsibilities or using any property or facility of NMC. All human subject studies 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 HHS.

The IRB may also, in its discretion, accept authority over studies for which IRB review is required under the regulations and in which members of NMC are participating, if review is requested by such member, even if the study will be conducted outside of, and without the involvement or support of, NMC.

The IRB may also, in its discretion or in the discretion of the IRB Chair on an expedited basis, accept the review and approval of another qualified IRB in limited cases where study-related activities at NMC are minimal.

**B.** The IRB shall review and approve all human subject research before it can be conducted by anyone else on the premises of NMC property or facilities. The IRB shall exercise its authority in full accordance with 45 CFR §46. This authority includes review and approval of exempt research under 45 CFR §46.104 (d); research, which qualifies for expedited review under 45 CFR §46.110; and research, which requires review by the full board. The IRB has the empowerment, flexibility and discretion to raise the standards of protection above those afforded to research subjects in 45 CFR §46 as it deems appropriate and necessary in particular cases although it may not lower the protections below those afforded by 45 CFR §46.

**C.** The IRB chair shall review all study applications and shall make a determination as to whether a study qualifies as Research or whether it does not.

## IRB Membership

It is the policy of NMC that the IRB will include an appropriately diverse mixture of backgrounds and experiences in accordance with 45 CFR § 46.107. The IRB will adhere to the following policy:

**A.** The IRB shall have at least five (5) members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by NMC.

**B.** The members of the IRB shall represent a diversity of academic disciplines and have the necessary credentials to provide appropriate review of protocols submitted for review. The IRB shall also be sufficiently qualified through the diversity of its members, including consideration of race, gender, and cultural backgrounds and sensitivity to such as issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

**C.** In addition to possessing the professional competence necessary to review specific research activities, 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 that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, or individuals with impaired decision-making capacity, or 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.

**D. Regular Members.** Regular voting members of the IRB shall include (to the extent that these requirements are not already met by the "Ex-officio members" or in addition thereto):

1. At least one member whose primary concerns are in non-scientific areas;
2. At least one member whose primary concerns are in scientific areas;
3. At least one member not otherwise affiliated with NMC. The unaffiliated member must not:
    a. have a professional relationship with the Institution as an employee, consultant, volunteer faculty, or student, and
    b. be a family member (first and second degree relative), which has a professional relationship with NMC
4. Both men and women, to the extent that this result can be accomplished through nondiscriminatory efforts.

**E. Ex Officio Members.** The IRB shall have two (2) categories of *ex officio* members:

1. **Voting:** A member who holds a position or office at NMC, which qualifies them for membership on the IRB, unless removed by the Chief Executive Officer. This *Ex Officio* member shall consist of the IRB Administrator or designee.

2. **Non-voting:** NMC's Chief Compliance Officer will serve in an *ex officio* capacity to offer legal counsel to the IRB, unless the Chief Compliance Officer is not a licensed attorney. If the NMC Chief Compliance Officer is **not** a licensed attorney, and a matter merits legal consideration, the IRB shall retain the appropriate legal advice.

**F. Alternates.** Alternates are appointed and function in the same manner as primary IRB members. The alternate's expertise is comparable to those of the primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the primary member(s) for whom each alternate member may substitute. The alternate member will **not** be counted as a voting member unless the primary member is absent. The IRB minutes will document when an alternate member replaces a primary member.

**G. Disqualification of IRB Members (Conflicts of Interest).** It is the policy of the IRB to identify and appropriately manage all IRB member potential conflicts of interest.

No member of the IRB shall participate in the IRB's review of monitoring (nor be counted toward a quorum for such purpose) of any study if:

1. Such member is directly associated through an
    a. immediate family relationship
        i. Parent or spouse of a parent, spouse, biological or adopted child, or anyone that may be claimed as a dependent under the Internal Revenue Code.
    b. professional association (partnership or professional corporation), or
    c. financial interest with the sponsor or Investigator, or

2. Such member is or was directly involved in the study under review; or

3. Such member's selection for a position on the IRB, in the case of a regular member, was participated in by the sponsor or Investigator; or

4. Such member is an advisor/mentor (e.g., thesis/dissertation/capstone), committee member and/or formally reviews a student proposal, or a direct faculty member of student's research (e.g., graduate or undergraduate student).

5. Such member (or immediate family member) holds a paid or unpaid position as director, office, partner, trustee, or any other significant position (e.g., scientific advisory board/consultant) in the company sponsoring the research or with a company with a financial interest in the product or service being tested.

6. Such member (or immediate family member) has a financial interest in a company, which has a marketed product, or is in the process of developing a new product, which is, or will be, in direct competition with the product in the protocol under IRB review.

Prior to the beginning of each meeting, IRB members will be asked to declare, but are not required to describe, any conflict of interest related to the protocols under review, which already have not been declared.

Although an IRB member has a conflict of interest, he/she will remain a member of the IRB; however, he/she cannot participate in the review and approval process for any project in which he/she has a conflict of interest. In cases where the assigned initial reviewer has a conflict of interest, the IRB protocol is reassigned to another reviewer.

When the member has a conflicting interest, he/she will not be present during final discussion and vote, and may be present only at the beginning of the meeting to provide information if requested by the IRB. He/she must be absent from the meeting room during the subsequent discussion and voting phases of the review and may not participate in the vote. The absent member is not counted towards a quorum when the vote on the protocol in question is taken. Minutes must reflect whether these requirements have been met.

The IRB meeting minutes will record the name of the IRB member with the conflict of interest and indicated that he/she was recused and did not vote.

**H. Vacancies.** Vacancies on the IRB may be filled by the NMC IRB Administrator and/or IRB Chair under the direction and authority of the Chief Executive Officer upon recommendation of the IRB.

**I. IRB Administrator.** The Chief Executive Officer shall appoint the Provost/Vice President of Academic Affairs (VPAA) to serve as IRB Administrator, who shall be responsible for overseeing the activities performed by the IRB. In the event that the Provost/VPAA position is vacant, the Chief Executive Officer will assume the role of IRB Administrator during the vacancy.

**J. IRB Chair**. The IRB Administrator shall appoint a faculty member to serve as Chair of the IRB, who shall have and exercise all duties that are traditionally held by a committee Chair or are specifically granted by their guidelines or applicable regulations will have the authority to discharge the duties and responsibilities of the IRB Chair.

**K. IRB Consultants/Expert Advice.** It is the policy of the IRB that services of expert consultants will be retained as needed.

1. Either before or during review of a protocol, the IRB Chair, or the IRB itself will determine if there is a need for appointment of an expert consultant, either a scientist or non-scientist, in accordance with the provisions of 45 CFR §61.07(f).

2. Consultants will be selected from within NMC, as well as from outside NMC based upon the required expertise.

3. Consultants who attend an IRB meeting may not vote and are excused upon conclusion of discussion of the study in question.

4. Potential consultants will be queried and asked by the IRB Chair before the meeting as to whether they have any potential conflicts of interest in accordance with the guidelines provided in under the Disqualification of IRB Members (Conflicts of Interest) guidelines.

5. Consultants shall be required to sign a confidentiality agreement prior to reviewing any protocol or receiving detailed information regarding the study in question.

**L. Appointment**. Regular members of the IRB shall be recommended for appointment by the IRB and appointed by the IRB Administrator and/or IRB Chair under the direction and authority of the Chief Executive Officer. Regular members shall serve for one (1) or more terms of two (2) years each, or until they resign or are removed from the IRB.

To ensure representation from the entire college, membership distribution for regular members of the IRB shall be comprised from the following departments/divisions 1) Undergraduate Nursing, 2) Graduate Nursing, 3) Health Professions, 4) Arts and Sciences, 5) NMC Community (Professional development, CREATE, Office of Student Engagement, Business Office, etc.). An alternate member shall be designated for each regular member of each department/division.

**M. Orientation and Initial Training for New IRB Members.** It is the policy of the IRB to provide new IRB Members with an orientation and initial training that includes the information necessary to facilitate the performance of assigned responsibilities.

1. All new IRB members shall receive an orientation packet, which includes the following materials:
    a. IRB Membership Roster
    b. Code of Federal Regulations: 45 CFR § 46
    c. IRB Policy Manual (includes the Belmont Report)
2. All new IRB members will be expected to successfully complete the Good Clinical Practice and the Social Behavioral Modules of the Collaborative Institutional Training Initiative (CITI) online training course, currently offered through Nebraska Methodist College and provide documentation of such certification to the IRB Manager or IRB Chair.

**N. Continuing Education Requirements for IRB Members.** It is the policy of the IRB to provide IRB members with ongoing continuing education. Ongoing training shall include:

1. Informational discussions and new articles provided at IRB meetings.
2. Periodic special meetings with guest speakers on legal, ethical or operational topics.
3. Opportunities to attend local, regional, or national seminars.
4. CITI certification is valid for two (2) to three (3) years, depending on the member's profession. When re-certification is required, IRB members must complete the continuing education modules available through the CITI-based training program and provide documentation of successful completion and re-certification to the IRB Manager or IRB Chair.

## IRB Meetings

It is the policy of the IRB to conduct *full board* meetings in compliance with the HHS regulations at 45 CFR §46.108(b).

1. A *full board* meeting cannot be convened without the presence of a quorum. A duly constituted quorum must include a simple majority of the voting membership and meets both *numerical* and *compositional* quorum requirements. The minutes reflect what capacity each member is serving for that meeting.
   a. **Numeric Quorum.** A necessary numerical quorum shall consist of a majority of the members of the IRB.
   b. **Compositional Quorum.** One person whose area of primary concern is non-scientific must be present at each meeting.

2. The IRB has a minimum of nine (9) regular voting members, plus one (1) non-voting ex-officio member serving as a legal representative.

3. No motion shall pass unless a ***simple majority*** of the IRB members, which constitute a quorum are present (in person, audio or video conference, or web with video exchange) during the discussion and vote in favor of the motion. If a member must leave the meeting *temporarily* (e.g., answer a call) before the vote is taken, the vote can be delayed. Voting by absentee is not permitted. If a motion fails to pass by a simple majority vote, other motions will be entertained.

4. At the discretion of the IRB Chair, voting may be by written ballot, a show of hands, or voice vote. The official meeting minutes will record, without individual identification, the number of votes to approve, disapprove, table, or abstain.

5. The IRB Manager or IRB Chair shall have the responsibility to monitor the members present at the convened meetings and determine that meetings are convened appropriately and remain so.

6. **Minutes and Reports.** Minutes of all regular and special meetings of the IRB shall be taken and preserved reflecting the action taken at the meetings. Each investigational plan and all supporting and related documents and correspondence as well as the written credentials of Investigators and IRB members, shall become a part of the permanent records of the IRB. The IRB shall retain all records until at least three (3) years after completion of the research to which the records relate.

7. The IRB shall schedule and hold regular meetings at times to be determined by the IRB Chair. The IRB Chair may schedule and hold special meetings at such other times as may be necessary to discharge the duties of the IRB. Special meetings may be called by the IRB Chair's initiative, or at the request of any IRB member or any NMC official involved in a study under the IRB's authority.

8. If attendance at a convened *full board* meeting falls below a quorum, the meeting will be adjourned and reconvened at the earliest possible time.

**Authority of IRB Chair between Meetings.**
The IRB Chair shall have authority to take the following actions during the period between meetings of the IRB, either alone or with the assistance of a standing or *ad hoc* committee appointed by the IRB Chair. The IRB Chair may:

1. **Exempt Review:** Review and approve applications for exempt review in accordance with the Exempt Review guidelines provided herein.

2. **Expedited Review:** Review and approve any applications for expedited review in accordance with the Expedited Review guidelines provided herein.

3. **Other Authority.** Take any other action and exercise any other authority delegated to him or her by the IRB, or in this IRB Policy Manual.

The IRB Chair may consult any other IRB member in his or her discretion before executing his or her responsibilities.

**IRB Minutes**

1. The IRB minutes will include
   a. core minutes, and
   b. detailed review letters to investigators, which are cited as addenda in the core minutes and thus, are an official component of the minutes.

2. The core IRB minutes will identify the IRB members who are present, IRB alternates who are serving to replace an IRB primary member, IRB alternates who are non-voting and are present, consultants, administrative staff who are present, and any guests in attendance at the meeting.
   a. Core minutes will include a record of alternate members who are serving in the place of a primary member.
   b. Minutes may also include justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document.

3. The core IRB minutes will include 1) the names of IRB members who have a conflict of interest and are recused (absent) from the discussion and the vote, and 2) a notation indicating that a conflict of interest was the reason for the absence.

4. The core IRB minutes will include the names of IRB members who do not have a conflict of interest, but are absent from the room at the time of the vote.

5. The core IRB minutes will include the vote counts for all board actions (e.g., for, against, and abstentions).

6. The core IRB minutes will include a written summary of the discussion and resolution of controverted issues. A controverted issue is clarified for the purposes of this policy as one, which generated a contentious discussion among members of the IRB over a human subject protection issue.

7. The core IRB minutes will include a determination of when continuing review is required more often than annually, as required by Health and Human Services regulations at 45 CFR §46.109(e). This determination will be based upon factors such as: the risk level of the research, inclusion of a vulnerable subject population, and a history of noncompliance.

8. The core IRB minutes will include the length of time of an approval for both full board and expedited protocols.

9. The core IRB minutes will include specific comments relevant to the inclusion of certain (e.g., vulnerable) populations.

10. The core IRB minutes will include an IRB determination of, which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review. This determination will be based on a history of noncompliance as well as other factors as the IRB deems appropriate.

11. In addition to the review of pending applications, meeting minutes may include information regarding expedited, continuing approvals, modifications, continuing reviews approved, exempt approvals, and any other business appropriate for IRB meetings.

12. The IRB minutes addenda (detailed review letters to investigators) will include the following:
    a. The basis for requiring changes in or disapproving research. IRB-required modifications of the initial IRB application, detailed protocol, consent/assent documents, requested clarifications, and additional information.
    b. IRB-required modifications of amendments to the IRB application and consent/assent documents.
    c. IRB-required actions in response to reports of unanticipated problems involving risk to the subject or others.
    d. Documentation of compliance with U.S Department of Health and Human Services regulations at 45 CFR§46.111(b), which require additional protections for vulnerable subjects, such as decisionally- impaired persons, economically or socially disadvantaged persons, and terminally ill patients.
    e. Documentation of IRB determinations involving waiver or alteration of Informed Consent, in accordance with Health and Human Services regulations at 45 CFR §46.116(d) including protocol-specific findings justifying those determinations.
    f. Documentation of IRB determinations involving a waiver of the requirement for obtaining a signed consent form in accordance with Health and Human Services regulations at 45 CFR §46.117(c)(1)(2)

13. The Chief Executive Officer and all IRB members shall have access to complete copies of IRB minutes, which include the appended IRB review letters. The letters are also kept on file in the IRB Chair's office and can be reviewed as requested.

14. The complete IRB minutes will be provided to Office for Human Research Protection (OHRP), auditing groups, and the courts in accordance with all applicable federal, state, and institutional requirements.

## IRB Member Responsibilities

1. Regularly attend scheduled IRB meetings and special meetings as called.

2. Review materials provided in advance of meetings as necessary to fully and meaningfully participate in the IRB's review and action on new studies, monitoring of ongoing studies, and other IRB actions. Members assigned as primary reviewers on some but not all studies may receive materials on the other studies also, and may review those materials prior to the meeting, at their discretion.

3. Participate on committees and subcommittees when appointed by the IRB Chair.

4. Complete Collaborative Institutional Training Initiative (CITI) training as identified in the Orientation and Initial Training for New IRB Members and Continuing Education Requirements for IRB Members of this IRB Policy Manual.

5. Maintain the confidentiality of all information coming before the IRB.

6. Disqualify (recuse) themselves from action on studies where the member has a conflict of interest as described in Disqualification of IRB Members (Conflict of Interest) guidelines.

7. Advise the IRB Chair of any concerns regarding IRB operations or regarding any studies, assist in the identification and development of improved IRB policies, procedures and standards and recommend to the IRB Chair any prospective candidates for appointment to the IRB.

8. Support, promote and carry out the mission of the IRB to protect human research subjects and the policies, procedures and standards set forth in this Policy Manual.

9. Serve as primary or secondary reviewer for 1) new studies; 2) applications for continuing review; 3) internal unanticipated problems involving risk to the subject or others; 4) external adverse events or serious problems; and 5) changes in studies and/or consent documents.

10. Serve as an exempt and expedited reviewer.

**IRB Member Confidentiality**

1. All IRB members will keep confidential all research studies and other information pertaining to research reviewed by the IRB, which is unavailable to non-IRB members.

2. All IRB review material must be secured in a locked personal file cabinet, or disposed of in a manner, which preserves confidentiality. IRB material should not be left unsecured in the IRB meeting room. Materials are left in the room at the end of the meeting for proper filing/shredding by IRB staff.

3. Protocols **without** a proprietary information/confidentiality restriction may be discussed with expert internal or external consultants. In such cases, NMC IRB staff should be notified. Confidentiality should be safeguarded by assigned consultants.

4. In the case of protocols **with** a proprietary information/confidentiality restriction, which required consultation with an internal or external consultant, the appropriate IRB staff should be notified in advance and approval obtained from the IRB Chair. Confidentiality should be safeguarded by assigned consultants.

5. All IRB members will have signed an IRB Confidentiality Agreement, which will be maintained in the appropriate IRB Chair's office.

## IRB Records

Under Health and Human Services regulations at 45 CFR §46.115, the IRB will maintain documentation of all IRB activities.

**A.** Where appropriate, the IRB Chair's office will maintain all records, reports, and other required documents as specified by federal regulations and NMC policies on record retention. The following documentation will be maintained for a minimum of three (3) years following the closure of the study for the purpose of IRB approval:
1. Copies of all research protocols reviewed.
2. Scientific evaluations, if any, which accompany the protocols.
3. Progress reports submitted by research investigators.
4. Reports of injuries to subjects.
5. Reports of unanticipated problems involving risk to subjects (including adverse event reports) and documentation of IRB review of these reports.
6. Minutes of IRB meetings.
7. Records of continuing review activities.
8. Copies of all correspondence between the IRB, the IRB office, and the research investigator.
9. List of IRB members and alternates.
10. DHHS-approved sample consent documents.
11. Statements of significant new findings provided to subjects.
12. Records pertaining to research, which is conducted, must be stored securely in the IRB Office and must be retained electronically or in printed form for at least 3 years after completion of the research. IRB records not associated with research or for research studies cancelled without subject enrollment will be retained at the facility for at least three (3) years after closure.

**B.** The IRB research study files will include:
1. IRB application (and all required documentation).
2. A copy of the investigator's current CITI certification.
3. Annual Continuance Request Report (as appropriate).
4. Request for Modification form (as appropriate)
5. Conclusion of Study Report
6. Federal grant applications (as appropriate).
7. Approved informed consent/assent documents (as appropriate).

8. Initial IRB review letter to the Investigator, including citations of appropriate federal regulations utilized during IRB review of research involving: prisoners (45 CFR §46 Subpart C) and/or children (45 CFR §46 Subpart D).
9. Investigator response to the IRB review letter.
10. Further correspondence regarding IRB review of the application.
11. Final IRB approval letter. The letter must include documentation of approvals under Health and Human Services regulations for *exempt* status [45 CFR §46.104(d)], and *expedited continuing* status [45 CFR §46.110].
12. IRB approval of recruitment materials and copies of the IRB approval materials.
13. All requests for changes and the correspondence pertaining to the request. Copies of the modified IRB approved and stamped consents and/or protocols associated with the request.
14. All Continuing Reviews and the correspondence pertaining to the request. Copies of the consent documents approved in conjunction with continuing review.

**C. Exempt protocols:** For studies granted exempt status, the file will include documentation of the exemption. Documentation of verified exemptions consists of the reviewer's citation of a specific exemption category and written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exemption category. The exempt determination is reported at the next convened IRB meeting and documented in the minutes.

**D. Expedited protocols**:
IRB records for initial review by the expedited procedure must include the specific permissible category, a description of action taken by the reviewer, and any determinations required by the regulations including protocol-specific findings supporting those determinations.

**E.** IRB records also must document any determinations required by the regulations and protocol-specific findings supporting those determinations, including:
1. Waiver or alteration of the consent process.
2. Research involving pregnant women, fetuses, and neonates.
3. Research involving prisoners.
4. Research involving children.

**F.** All interim progress reports.

**G.** Reports of unanticipated problems (internal adverse events, internal fatal adverse events, external adverse events, and unanticipated problems involving risk to the subject or others) and the correspondence pertaining to the reports. (Copies of supporting documentation and consent documents will be attached to the report.)

**H.** Incidents of noncompliance, including documentation of investigation, correspondence, and reports to institutional officials and OHRP, where appropriate.

**I.** Results from correspondence regarding the findings.

**J.** IRB records for initial and continuing review by expedited continuing procedure include:
1. The specific permissible category.
2. Description of action taken by the reviewer.
3. Any determinations required by the regulations, along with protocol specific findings justifying those determinations.

**K.** Paper copies of the IRB research study records are maintained in the IRB Chair's office until the protocol is completed or terminated. The complete file is maintained in the terminated files until three years after the original termination date. Once a year (or more often as necessary), these files are scanned and archived on our secure server.

# IRB REVIEW CATEGORIES AND DECISIONS

## IRB Review Categories

| EXEMPT | EXPEDITED | FULL BOARD |
|---|---|---|
| No greater than minimal risk to human subjects<br><br>**AND**<br><br>Fits into one of the categories of *Exempt* research per Federal Guidelines | No greater than minimal risk to human subjects<br><br>**AND**<br><br>Fits into one of the categories of *Expedited* research per Federal Guidelines | Minimal or greater than minimal risk to human subjects<br>**OR**<br>Does not meet criteria and/or eligibility for *Exempt* or *Expedited* Review<br>**OR**<br>As determined by the IRB Chair |

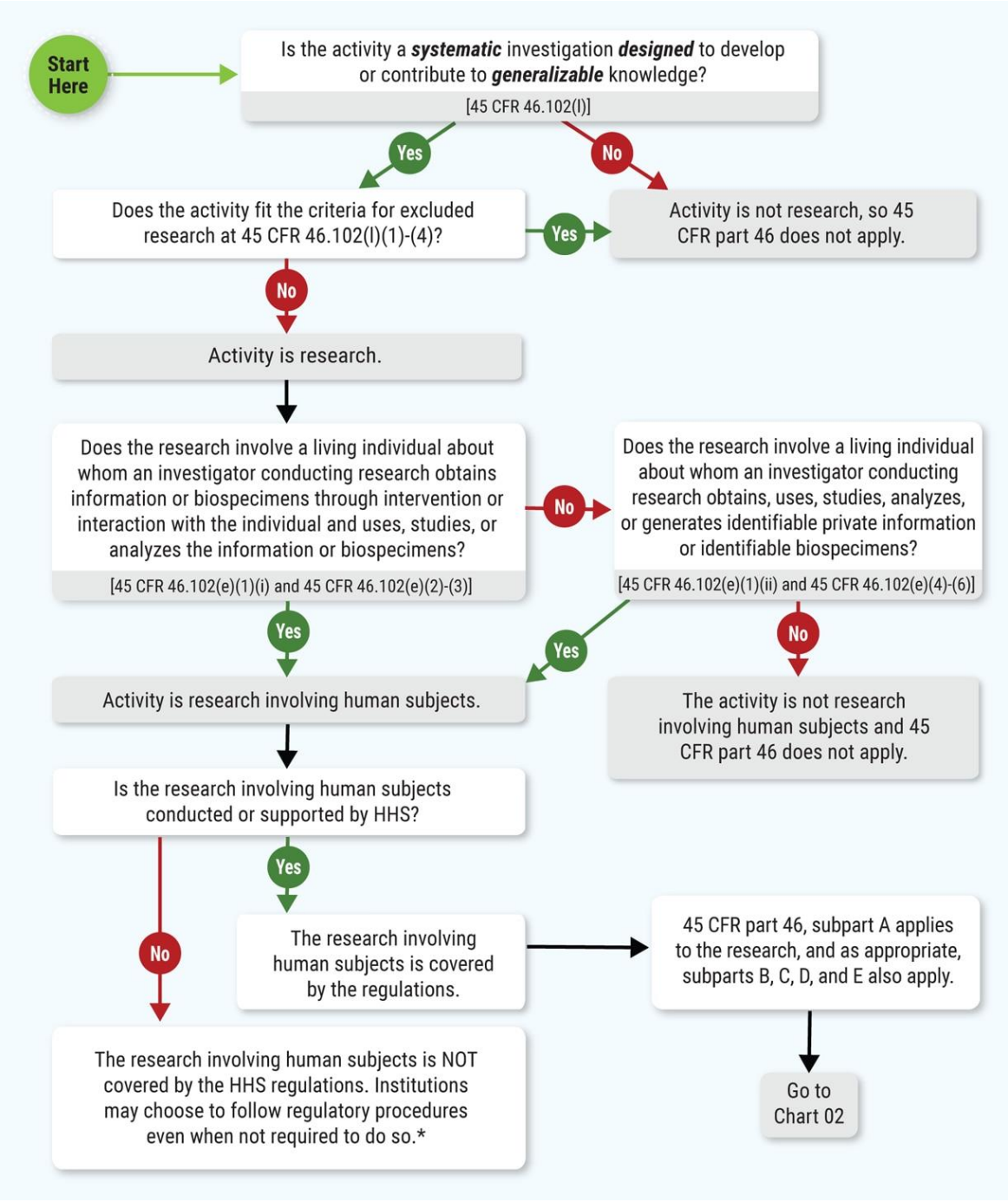
| TYPE OF RISK | DEFINITION |
|---|---|
| **"No greater than minimal risk"** | The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. |
| **"Greater than minimal risk"** | Risk of harm or discomfort is beyond that normally encountered in daily life (Invasive procedures, responding to stressful physiological or psychological testing). |

It is the policy of the IRB that all research must be appropriately classified as ***exempt, expedited, continuing, limited,*** or ***full board*** review in accordance with HHS regulations at 45 CFR §46.

The U.S. Department of Health and Human Services, Office of Human Research Protection (OHRP) has published Decision Charts to help determine whether a particular activity constitutes research involving human subjects.

**See Chart 1 to determine if proposed research protocol involving human subjects is covered under 45 CFR part 46.**

## *Chart 1: Is an Activity Research Involving Human Subjects Covered by 45 CFR part 46?*



## Exempt Review

All proposed ***exempt*** research may be reviewed by the IRB Chair between meetings and without *full board* approval, to determine whether the research meets at least one of the categories of exemption from the federal regulations for the protection of human research subjects in accordance with HHS regulations at 45 CFR §46.104(d).

All ***exempt*** research involving human subjects must maintain an ethically appropriate standard, which serves to protect the rights and welfare of the subjects. This involves informed consent as necessary and confidentiality of data. In some ***exempt*** research projects, standard written informed consent must be obtained.

***Exempt*** research, once approved, does not require annual review. Projects that are approved as *exempt* are valid for five years.

All modifications of protocols including *exempt* research must be submitted to the IRB. ***Exempt*** research, which requires modification during the course of the study whereby it is no longer *exempt,* must be resubmitted to the IRB prior to implementation of the modification.

The IRB Chair reserves the right to refer applications for *exempt* research to either the *expedited review* procedure or the *full* IRB for review as necessary.

If a submitted proposal qualifies for *exempt* status in accordance with HHS regulations at 45 CFR §46.104(d) (1-8), the proposal will be reviewed using the *exempt* review procedure once the proposal is assigned into one of the eight (8) *exempt* categories.

**Ineligible Research Populations (Do Not Qualify for Exemptions)**

1. Sensitive survey research that is identifiable where the disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

2. The research involves survey, interviews, or subject observation with children.

3. Research involving prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons,

4. Other subject populations determined to be vulnerable upon review:
   a. Frail elderly
   b. Pregnant woman, human fetuses, and neonates
   c. Victims
   d. Individuals receiving HIV testing or have been diagnosed with AIDS

**Ethical Considerations**

Although *exempt* research is not covered by the federal regulations, this research is not *exempt* from the ethical guidelines of the Belmont Report. The individual making the determination of exemption may require additional protections for subjects in keeping with the guidelines of the Belmont Report.

**Eight (8) Categories of research eligible for exempt status:**

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are least likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on (1) regular and special education instructional strategies; or (2) research on the effectiveness of or the comparisons, among instructional techniques, curricula, or classroom management methods.

   Educational research proposals are *exempt* providing all of the following conditions are met:
   a. All of the research is conducted in a commonly accepted educational setting (e.g., public school).
   b. The research involves normal educational practices (e.g., comparison of instructional techniques).
   c. The study procedures do not represent a significant deviation in time or effort requirements from those educational practices already existent at the study site.
   d. The study procedures involve no increase in the level of risk or discomfort attendant in normal, routine educational practices.
   e. Provisions are made to ensure the existence of a non-coercive environment for those students who choose not to participate.
   f. The school or other institution grants written approval for the research to be conducted.

   ***NOTE: Educational projects that do not meet the above-listed conditions are not exempt and must undergo expedited, continuing, or full board review.***

2. Research only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met: The information obtained is recorded by the investigator in such a manner that the identity of human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects
   a. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.
   b. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

   ***NOTE: Research that involves photographing, audiotaping, or videotaping of subjects during the research may be granted an exemption with some discretion as it relates to identifiability or sensitivity of the research. Projects involving photographing, audiotaping, or videotaping will be reviewed on a case by case basis to determine the risk in relation to the identifiability of the photographs, audios, and/or videos along with the sensitivity of the questions being asked. The use of scrambling technologies, such as voice alteration or blurring/masking, also will be taken into consideration.***

   ***NOTE: Projects involving oral histories are not considered research***

3. Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
   a. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects.
   b. Any disclosure of the human subjects' responses outside of the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.
   c. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §46.111(a)(7).

   For the purposes of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find interventions offensive or embarrassing. Provided all such criteria is met, examples of benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

   If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
   a. The identifiable private information or identifiable biospecimens are publicly available.
   b. Information, which may include information about biospecimens, is recorded in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.
   c. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that is regulated for the purposes of "health care operations" or for "public health activities and purposes".
   d. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads ( or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to

conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants.

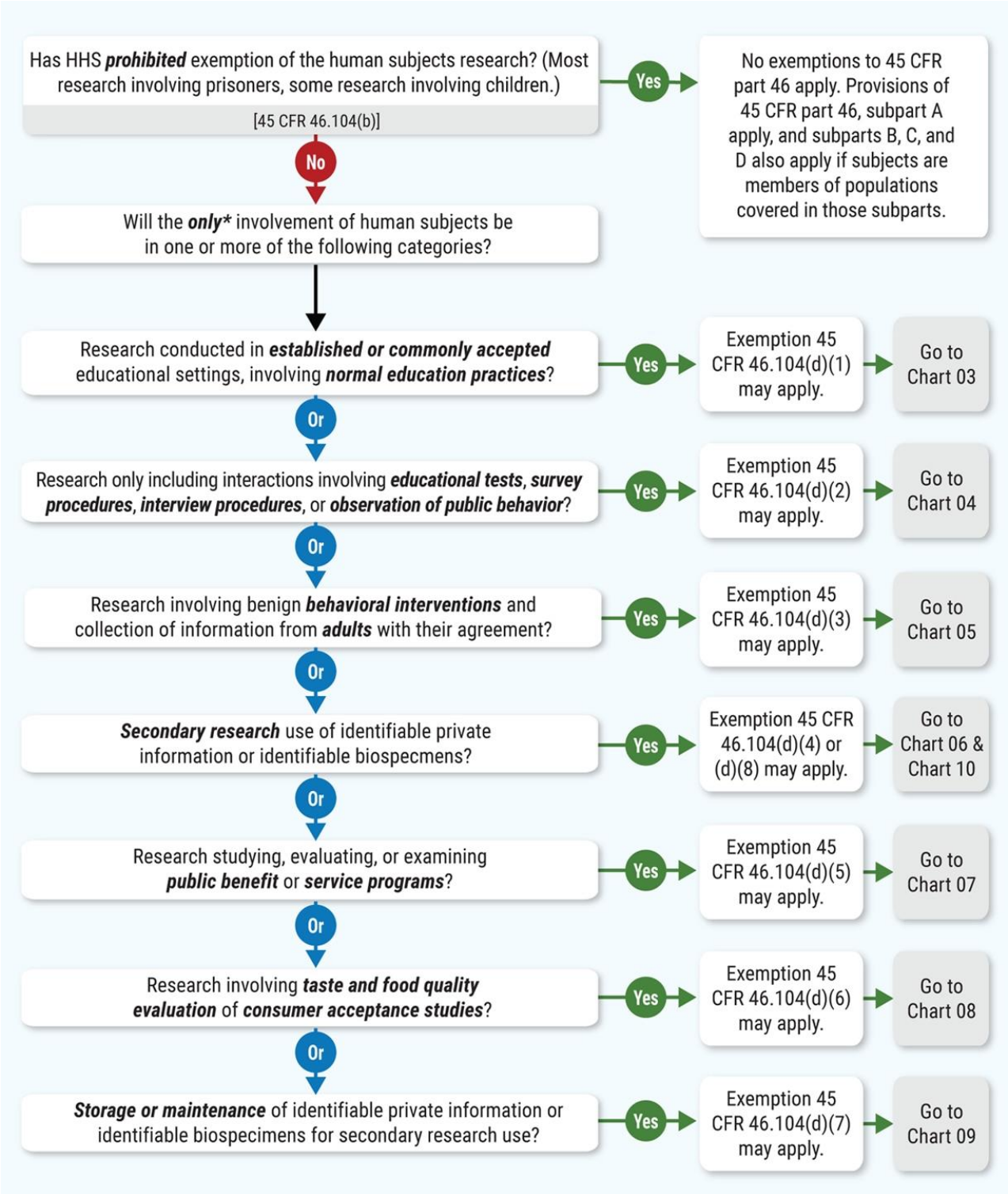
6. Taste and food quality evaluation and consumer acceptance studies, if (1) wholesome foods without additives are consumed, and (2) a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration, or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited review and makes the determinations required by §46.111(a)(8).

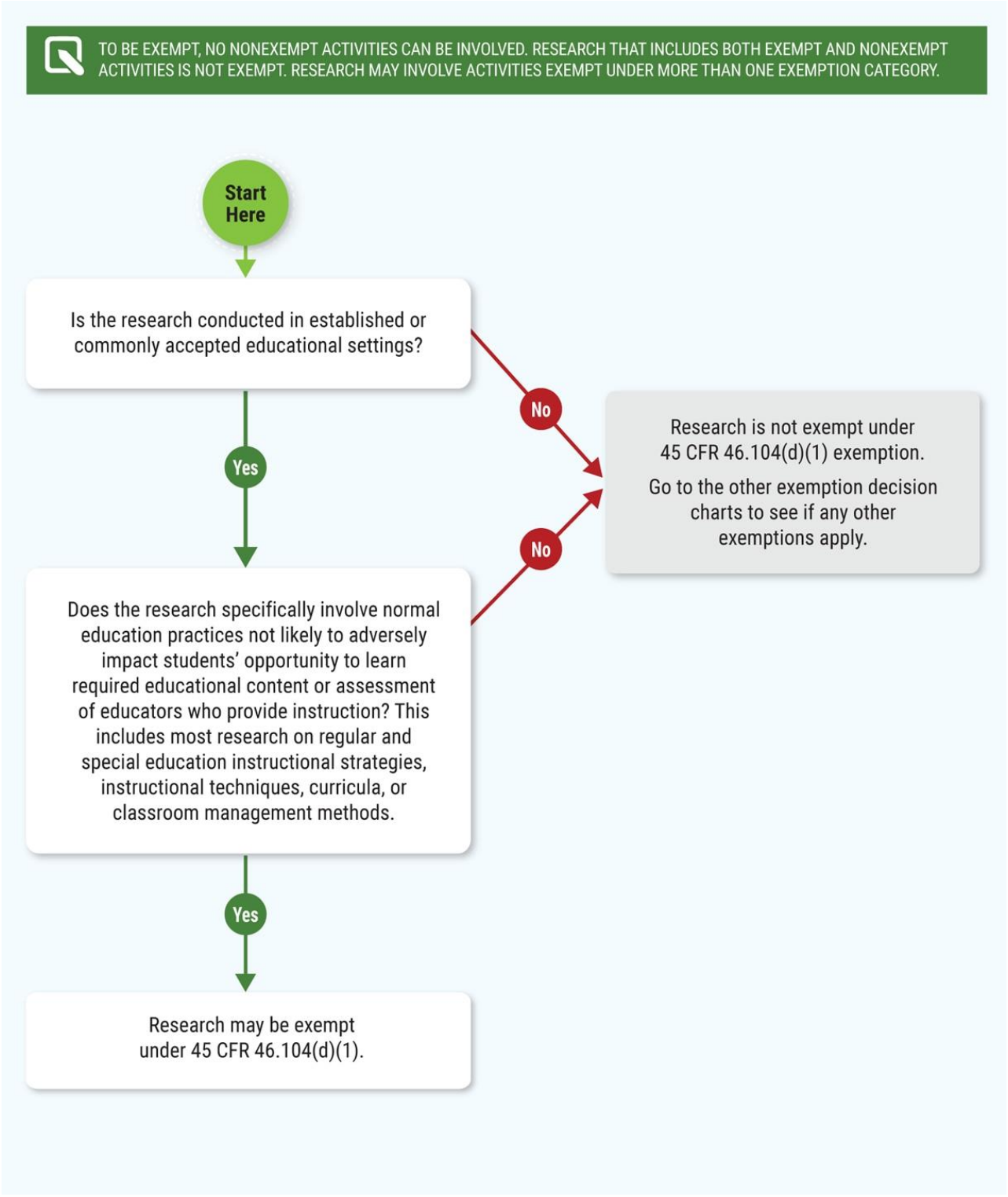
8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
   a. Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a) (1-4, 6) and (d).
   b. Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117.
   c. An IRB conducts a limited IRB review and makes a determination required by §46.111(a) (7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in §46.104(d) (8) (i); and the investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual results.

**See CHARTS 2 – 10 to determine if proposed research protocol is eligible for exemption under 45 CFR 46.104(d).**

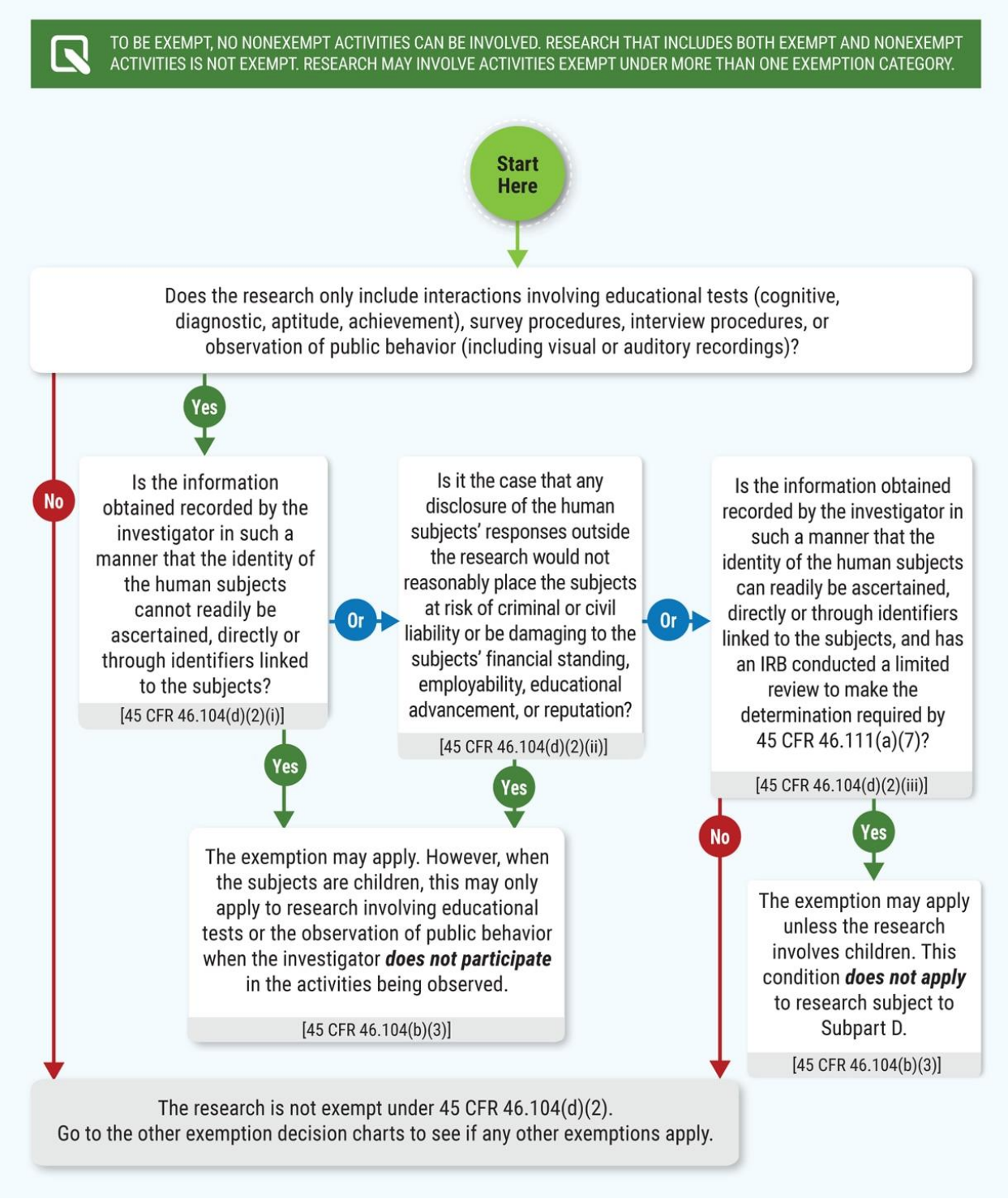
## *Chart 2: Is the Research involving Human Subjects Eligible for Exemption under 45 CFR 46.104 (d)?*



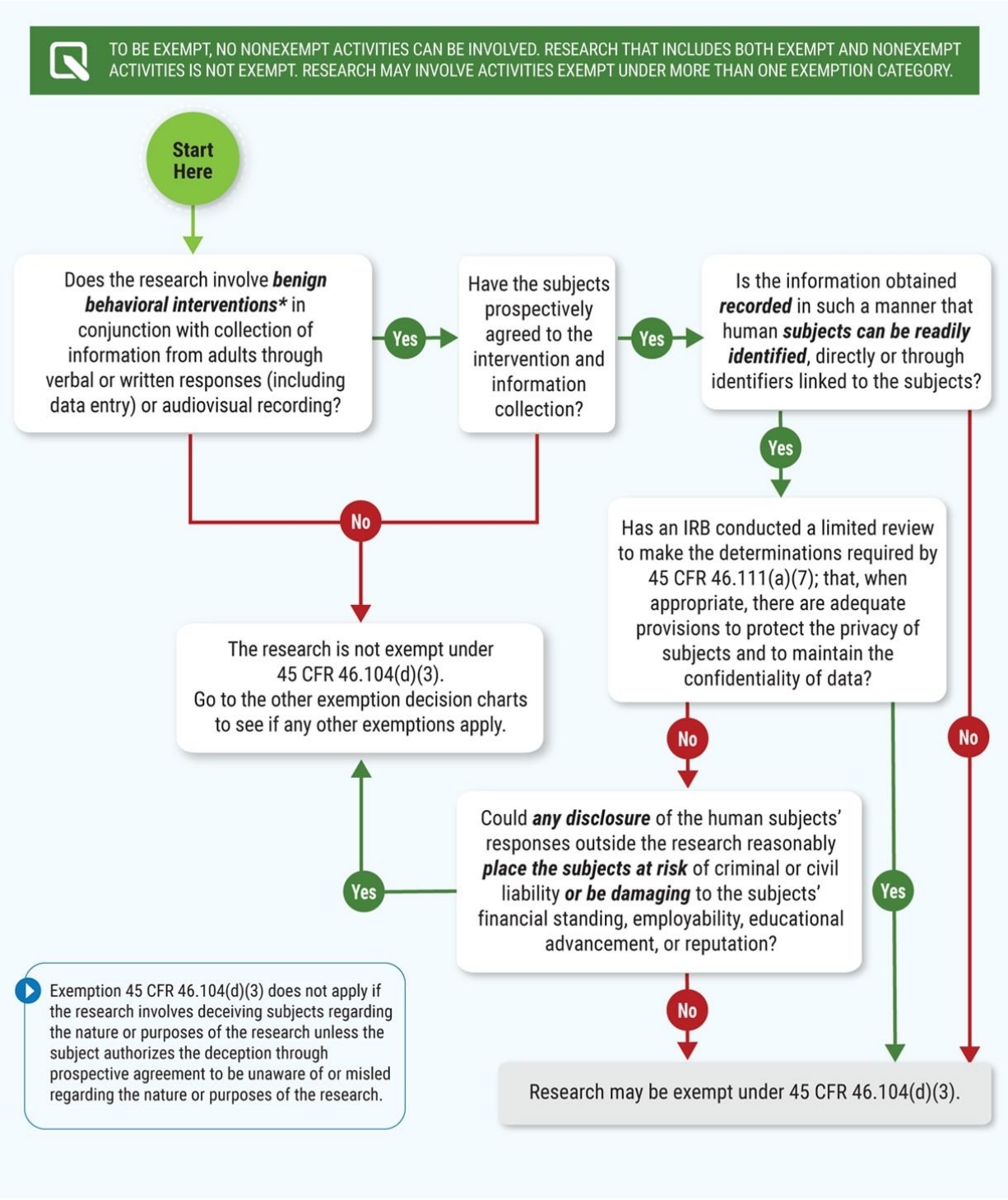
## *Chart 3: Does Exemption 45 CFR 46.104(d) (1) for Educational Practices Apply?*



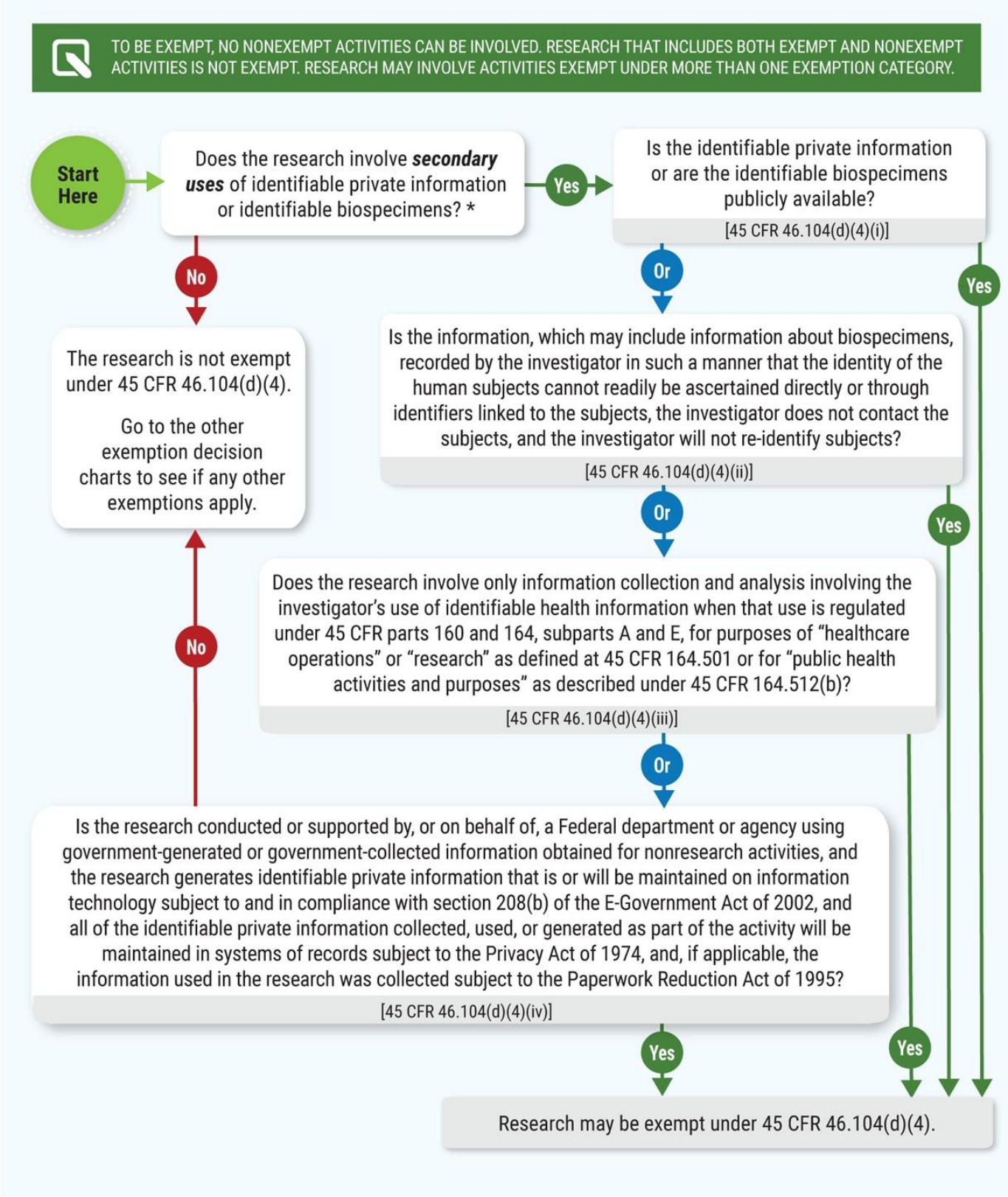
## *Chart 4: Does Exemption 45 CFR 46.104(b) (2) for Tests, Surveys, Interviews, or Public Behavior Observation Apply?*



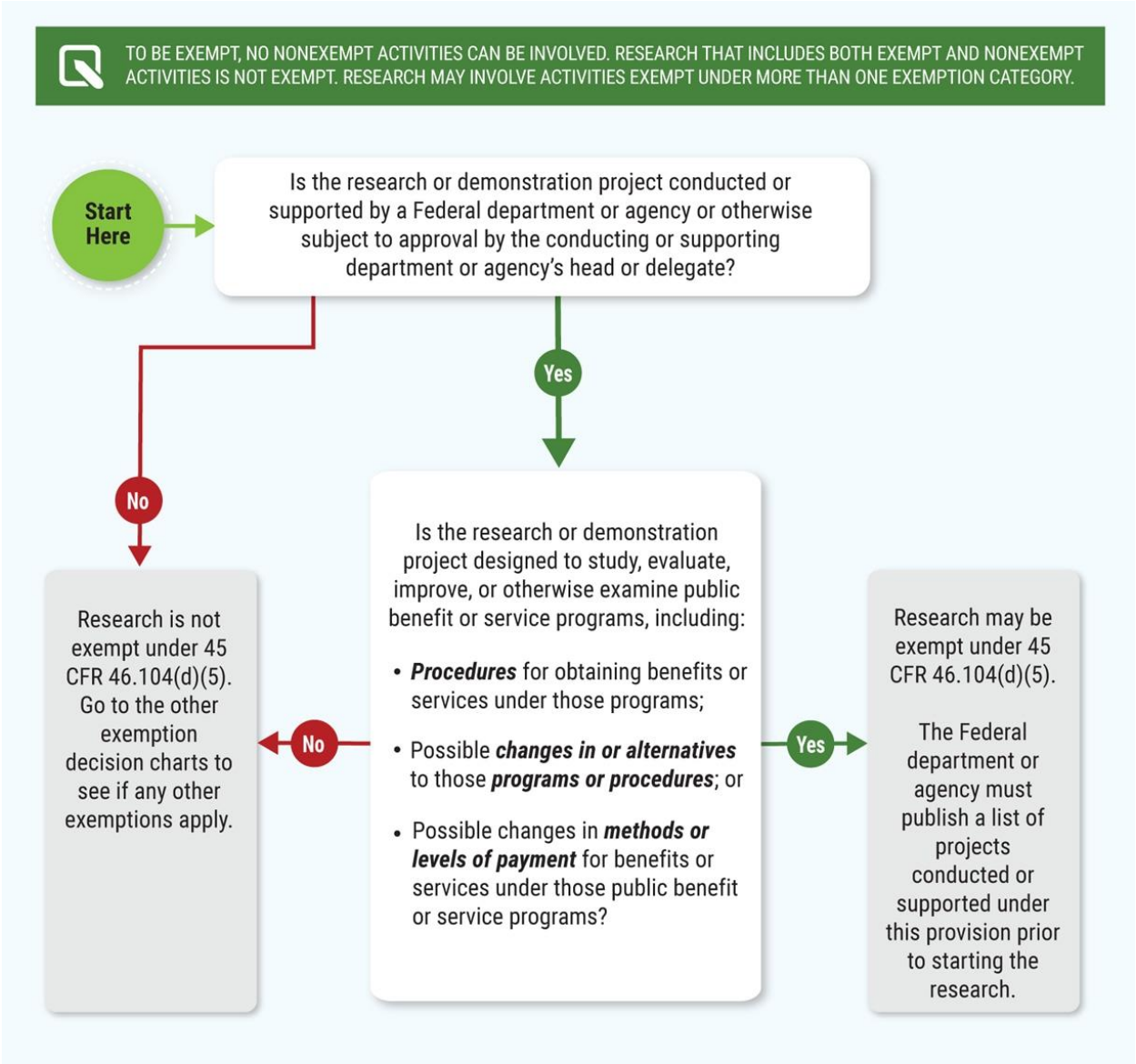
## *Chart 5: Does Exemption 45 CFR 46.104(d) (3) for Benign Behavioral Interventions Apply?*



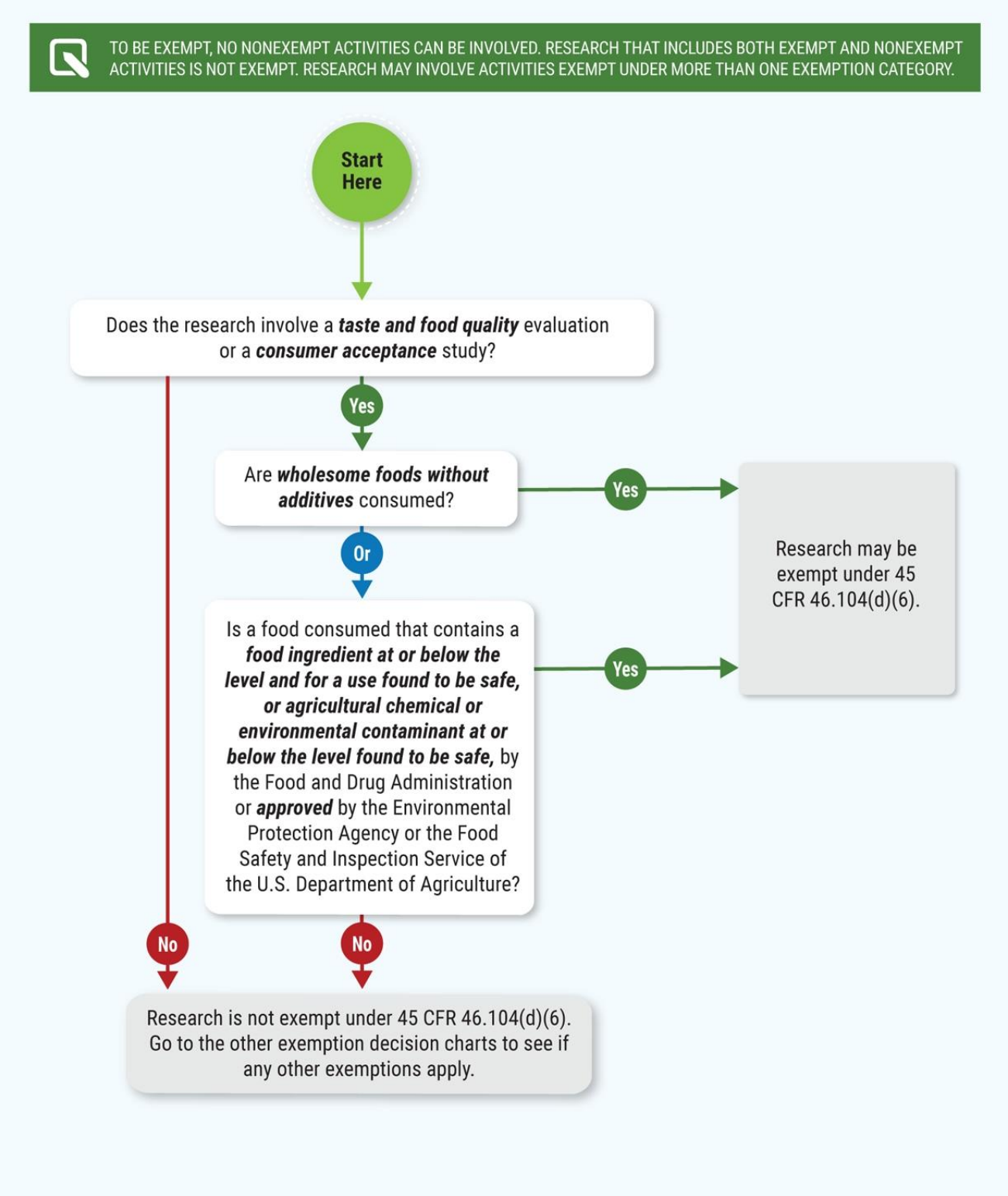
## *Chart 6: Does Exemption 45 CFR 46.104(d) (4) for Secondary Research that Does Not Require Consent Apply?*



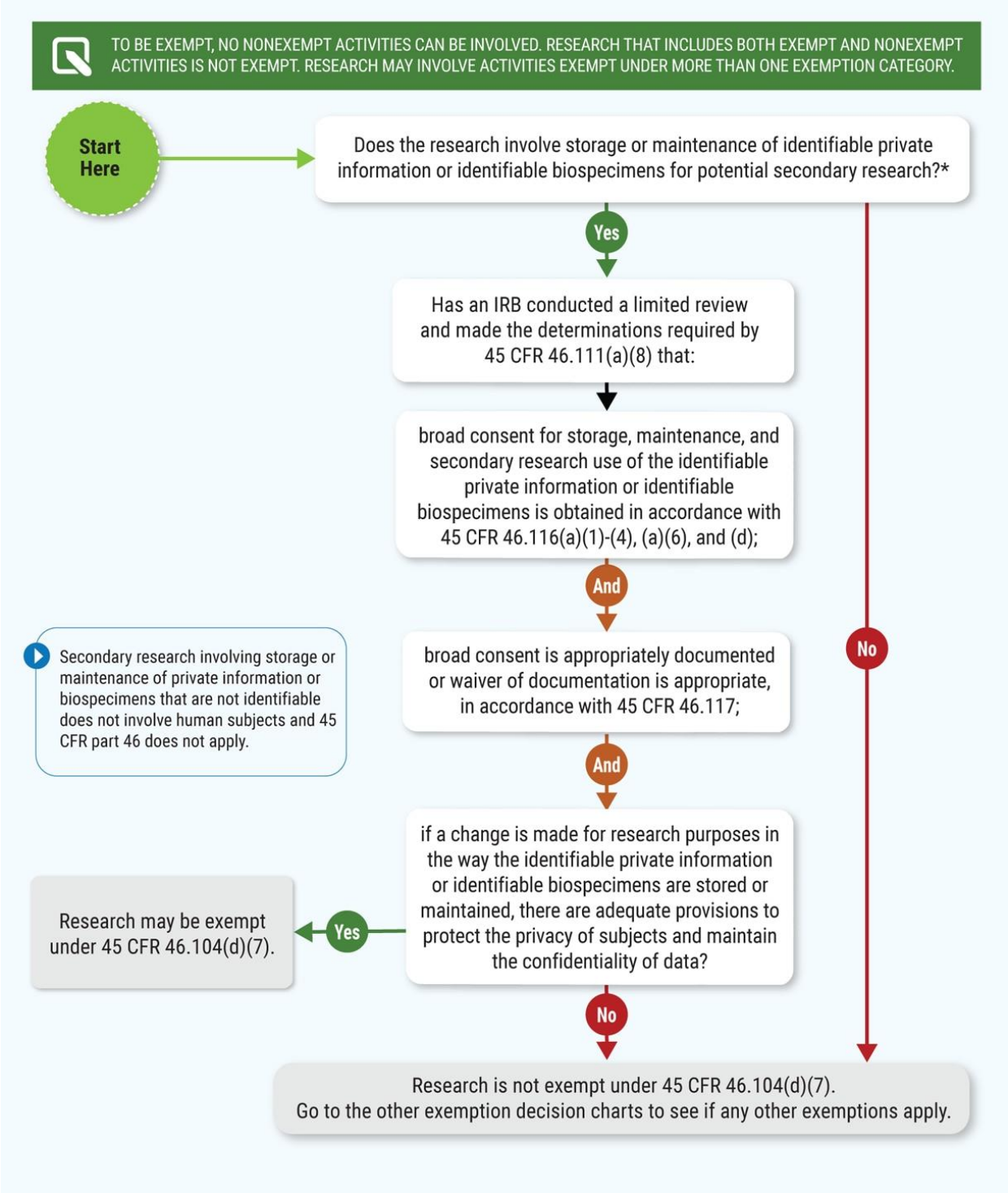
## *Chart 7: Does Exemption 45 CFR 46.141(b) (5) for Public Benefit or Service Programs Apply?*



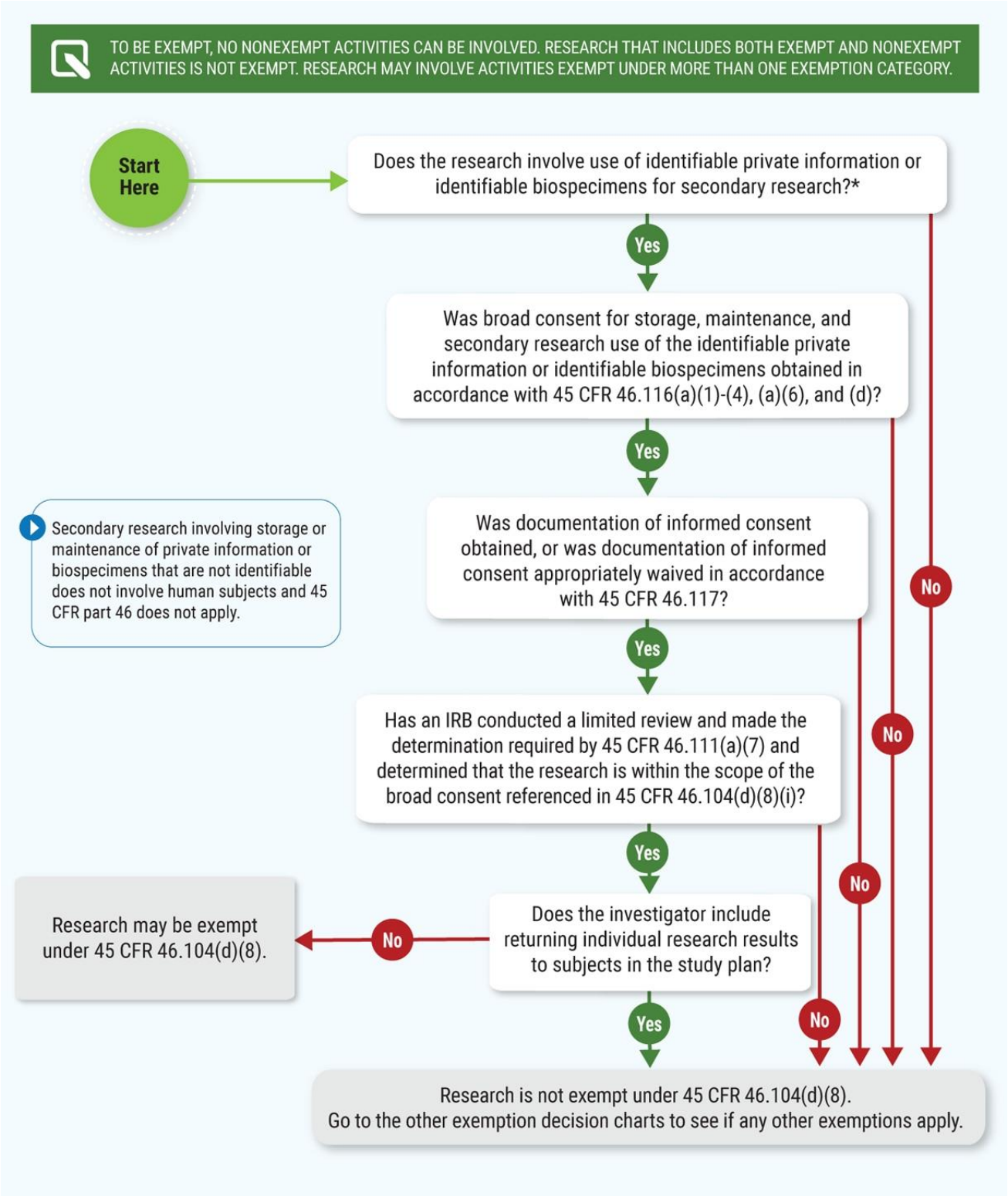
## *Chart 8: Does Exemption 45 CFR 46.104(d) (6) for Food Taste and Acceptance Studies Apply?*



## *Chart 9: Does Exemption 45 CFR 46.104(d) (7), Storage for Secondary Research for Which Broad Consent Is Required, Apply?*



## *Chart 10: Does Exemption 45 CFR 46.104(d) (8) for Secondary Research for Which Broad Consent Is Required Apply?*



## Expedited Review

Certain research activities involving minimal risk to subjects in initial reviews or minor changes in previously approved (continuing review) research may be reviewed and approved by the IRB Chair **without** full IRB approval. The IRB Chair reports such action to the full IRB, which may ratify, reverse or modify the IRB Chair's actions. The IRB Chair may decline to grant expedited review and refer the matter for full IRB review at any time. Disapproval of proposed research requires action by the full IRB. ***Expedited*** research, once approved, does not require annual review. Projects that are approved as *expedited* are valid for five years Studies approved on an expedited basis are subject to the same reporting requirements (modifications, adverse events) as other studies.

Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the expedited categories listed below, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR §46.110. 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 human subjects.

Three (3) applicable criteria must be met for the initial or continuing review of the expedited procedure using regardless of the age of subjects, except as noted.

1. The expedited review procedure 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 subjects 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.

2. The expedited review procedure may not be used for classified research involving human subjects.

3. The standard requirements for informed consent (or its waiver, alteration, or exception) applies regardless of the type of review--expedited or convened--utilized by the IRB.

**Expedited Research Categories**

1. Modifications of previously approved research where there is no material change to the risk-benefit analysis and where there is no material change to the informed consent document.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   a. From healthy, nonpregnant 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.

***Note: Health and Human Services regulations at 45 CFR 46.402(a) define children as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted."***

***Although according to Nebraska state statute # 43-303, "Child means an individual under nineteen years of age", this definition is irrelevant for determining which individuals under Nebraska law meet the DHHS definition of children. To determine under Nebraska law which individuals meet the DHHS definition of children, the relevant Nebraska laws define the legal age to consent to treatment or procedures involved in some research. In some cases, individuals such as emancipated minors or minors requesting treatment for contraceptives, venereal disease, or drug abuse, have reached the legal age under Nebraska law to provide consent. These individuals are "children" under Nebraska law, but are not "children" under DHHS regulations, in that the additional protections of Subpart D are not required because these individuals have reached the legal age to consent to the treatments or procedures involved in the research.***

3. 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. uncannulated 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 subgingival 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.

4. 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.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

   ***NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR §46.104(d) (7). This listing refers only to research that is not exempt.***

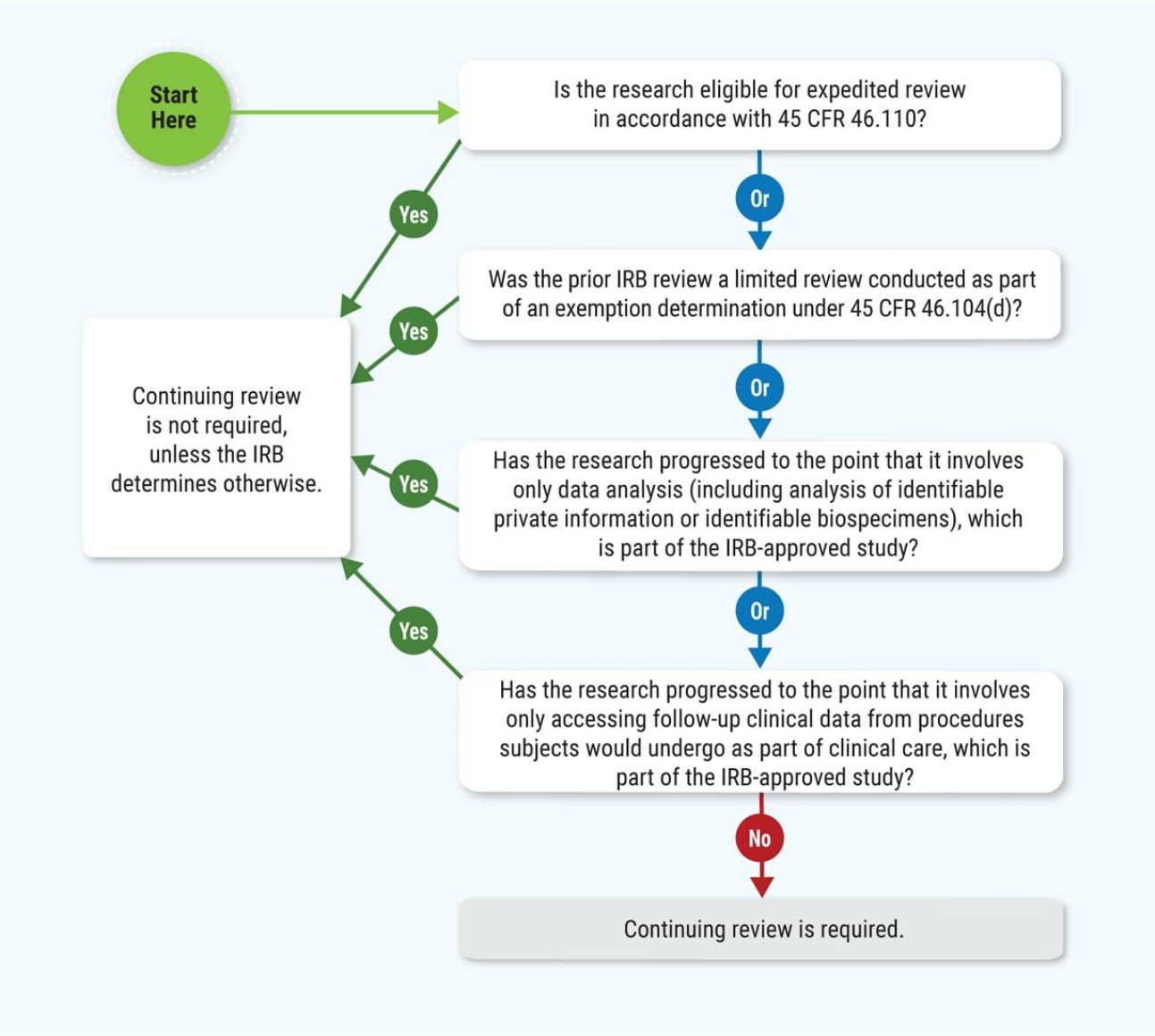
6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. 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 human subjects. 45 CFR §46.101(b) (2) and (b) (3). This listing refers only to research that is not exempt.)

8. 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.

**See CHART 11 to determine whether continuing review may be done by Expedited Procedures under 45 CFR 46.109 (f).**

## *Chart 11: Is Continuing Review Required Under 45 CFR 46.109(f)?*



## Review Criteria of Non-Exempt Research (Expedited and Full Board)

It is the policy of the IRB that all **non-exempt** research proposals (*expedited* and *full board*) will undergo a rigorous review which will allow a determination that the protocol meets the criteria specified in 45 CFR §46.111.

In considering whether to approve, conditionally approve, or disapprove a proposed study, the IRB shall consider, without limitation:

1. 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 or the regulations;

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

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

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

5. Whether the proposed study subjects human beings to undue risks. Risks considered will include physical and psychological risks, social risks such as risk to privacy interests, economic risks including direct and indirect costs to the patient, and in appropriate cases may include legal risks. In assessing risks, the IRB shall consider, among other things, whether:
   a. Risks to subjects are minimized: (i) By using procedures that are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
   b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
      i. 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 (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
   c. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
   d. 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 45 CFR §46.116.
   e. Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR §46.117.

f. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
g. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

6. Whether provision has been made in the study or by the IRB or others for prompt reporting to the IRB, the Investigator, appropriate NMC officials, the NMC, HHS, and/or the sponsor, of (1) unanticipated problems involving risks to human subjects or others, (2) information received concerning injuries to human subjects, (3) any changes in the study which are reviewed and approved by the IRB, (4) any instance of serious or continuing noncompliance with the regulations, or with the requirements or determinations of the IRB, or (5) any suspension or termination of IRB approval; and

7. 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 on the conduct of the study. Potential conflicts to be considered shall include, but not be limited to, significant financial interests of the Investigator in the research (Investigator Responsibilities and Standards) and conflicts that may be created by the payment of fees or other benefits to the study subject.

# IRB Decisions

**A. Expedited Review:**

After IRB Chair or IRB member reviews the research proposal by investigator, the investigator will be notified of the IRB's decision concerning the proposal. Reviewed proposals will be assigned one of three categories:

1. ***Approval and Full Release***
   The proposal is approved and released. The investigator may begin the study.
2. ***Approval with modifications***
   The proposal is approved contingent upon IRB Chair or, unless otherwise specified, IRB member reviewer acceptance of specific modifications and/or clarifications
   The investigator will be notified, in writing, as to the nature of the required modifications and/or clarifications. As soon as the investigator complies in writing with all requirements, a release will be issued and the investigator may begin the study.
3. ***Referred for full IRB review***
   The IRB Chair or IRB Administrator has a serious concern and has determined the proposal should be reviewed by the full IRB.

**B. Full Board Review**

Proposals that do not qualify for *exempt* or *expedited review* will be submitted to the full IRB.
After the IRB meeting, the investigator will be notified in writing of the IRB's decision concerning the proposal. In accordance with the IRB's decision, the IRB letter will specifically detail items requiring clarification, modification or justification. The investigator will be requested to respond to IRB concerns. The IRB minutes should reflect the IRB determination.

Reviewed proposals will be assigned to one of six (6) categories:

1. ***Approval and full release***
   No modifications or clarifications are required and the investigator may begin the study.
2. ***Conditional approval, contingent upon IRB Chair acceptance of specific modifications/clarifications***
   This category is restricted to modifications/clarifications that are not directly relevant to the regulatory determinations. The investigator will be notified in writing as to the nature of the required modifications and/or clarifications. When the investigator complies, in writing, with all requirements as determined by the IRB Chair, a release will be issued and the investigator may begin the study.
3. ***Conditional approval, contingent upon full IRB re-review of specific modifications/clarifications***
   This category is restricted to modifications/clarifications, which are considered substantive in nature. The investigator will be notified in writing as to the nature of the required modifications and/or clarifications. When the investigator complies, in writing, with all requirements as determined by the full IRB at a convened meeting, a release will be issued and the investigator may begin the study.

4. ***Tabled***
   This category is restricted to applications where the IRB requires a significant amount of additional information and/or has a serious concern. The investigator will be notified in writing of the IRB's decision concerning the proposal. The IRB Chair and/or a member of the Board may be assigned to discuss the proposal with the investigator. When the investigators submit the required materials for re-review, the tabled protocol will be reviewed at the next IRB meeting in adherence with published submission deadlines for *full board* meetings. Whenever possible, the IRB reviewers who performed the initial review will be assigned to re-review the protocol. When that is not possible, IRB reviewers are encouraged to consult, as necessary, with previous reviewers in order to resolve any problems or concerns, which may still exist.
5. ***Disapproved***
   This category is restricted to applications, which have very serious design flaws and/or subjects will be placed at undue risk. The investigator has the right of appeal to the IRB, which must be requested in writing. When necessary, the IRB will seek consultation from nationally recognized experts in the field, other IRBs, OHRP, and the National Science Foundation Office of the Inspector General (OIG). Every attempt will be made to resolve the identified problem(s). The IRB, however, retains final authority over whether or not a proposal can be approved.
6. ***Decline to complete the review***
   This category is restricted to applications, which are significantly deficient in information or content and adequate review of the protocol could not take place. The Application will be returned to the investigator with instructions to review and revise the application in consideration of application instructions and guidelines and resubmit the application to the IRB when ready.

**C. Limited Review**

Proposals that qualify for limited review are concerned with identifiable private information or identifiable biospecimens. For the purposes of conducting a limited review required by 104(d) (7), the IRB shall make the following determinations:

1. Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained.
2. Broad consent is appropriately documented or waiver of documentation is appropriate.
3. 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.

If the determinations are all made, the reviewed proposal will be assigned one of two categories:

1. ***Approval and Full Release***
   The proposal is approved and released. The investigator may begin the study.
2. ***Approval with modifications***
   The proposal is approved contingent upon IRB Chair or, unless otherwise specified, IRB member reviewer acceptance of specific modifications and/or clarifications. The investigator will be notified, in writing, as to the nature of the required modifications and/or clarifications. As soon as the investigator complies in writing with all requirements, a release will be issued and the investigator may begin the study.

3. ***Referred for full IRB review***
   The IRB Chair or IRB Administrator has a serious concern and has determined the proposal should be reviewed by the full IRB.

**D. Continuing Review**

It is the policy of the IRB that ***continuing*** review will be conducted in accordance with 45 CFR §46.109(e) and OHRP guidance on continuing review (July 11, 2002). Unless an IRB determines otherwise, continuing review is not required in the following circumstances:

1. Research eligible for expedited review in accordance with §46.110.
2. Research reviewed by the IRB in accordance with the limited IRB review described in §46.104.
3. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
   a. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
   b. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

Only ***full board*** protocols are required to have a continuing review conducted. Full board protocols are approved for one (1) year at a time and valid for up to five years but must be renewed annually by completion of an **Annual Continuance Request Application.** New enrollment of subjects is not allowed after the expiration of IRB approval.

In order for a study to continue without interruption, the IRB must re-review and approve the protocol ***prior*** to the IRB approval expiration date. Continuing Review has to occur as long as the research remains active for long-term follow-up of subjects, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions.

Continuing review of research has to occur when the remaining activities are limited to collection of private identifiable information. If an investigator does not provide continuing review information to the IRB, or the IRB has not approved the protocol by the expiration date, the investigator will be instructed to **SUSPEND** all research activities, including recruitment, enrollment, interventions, and interactions, and collection of private identifiable data, and to stop all interventions and interactions on current subjects, unless the IRB finds an over-riding safety concern or ethical issue involved such that it is in the best interests of individual subjects to continue participating.

**E. Risk Level**

All human subject studies are subject to ***continuing*** review based on the level of risk as assessed by the IRB. Projects that were initially reviewed by the ***full board*** continue to receive ***full board*** review unless the IRB determined at the initial review during the ***full board*** meeting that the study meets the specific criteria for ***expedited review***.

**F. Continuance Request Submission Requirements**

1. It is the responsibility of the Investigator to submit the Annual Continuance Request Application which must include informed consent/assent forms (updated as necessary) in sufficient time to allow the IRB to complete a substantive and meaningful review of the research, as well as provide the Investigator with a timely, written response prior to the expiration date indicated on the current IRB approval letter.

2. If the IRB, or *expedited reviewe*r(s), determines that a project requires review more often than annually, the investigator will be so notified at the time of initial review and/or at the time of continuing review.

**G. Expedited Continuing Review Procedure**

If the IRB, or expedited reviewer(s) determines that a protocol requires increased and/or more frequent monitoring, the records of continuing review activities must include the rationale for conducting continuing review of research.

**H. Expedited review Actions.**

1. ***Re-approval and full release***
   No modifications or clarifications are required. All of the criteria for IRB approval specified in Health and Human Services regulations at 45 CFR §46.111 are satisfied. The investigator will be notified of the re-approval in writing and is authorized to continue the study.
2. ***Re-approval and full release (with minor clarifications)***
   Minor clarification(s) or information concerning the protocol is necessary for completion of the record. This action is only taken when the clarification(s) is (are) minor and does not impact protection of human subjects and/or the approvability of the consent document(s). The investigator will be notified of the re-approval in writing and asked to make the necessary modifications and return the materials before final approval for continuing review can be granted. Failure to respond to the IRB continuing review clarification letter may result in the full IRB revoking approval of the study. In such a case, all research related activities must immediately cease, unless an extension is granted by the IRB Chair in consideration of a written request from the Investigator. The IRB will be notified of all extensions granted by the IRB Chair. The IRB Chair is empowered by the IRB to review the Investigator's response in and grant re-approval and full release.
3. ***Conditional approval,*** contingent upon Expedited reviewer acceptance of specific modifications/clarifications.

   The investigator will be notified in writing as to the nature of the required modifications/clarifications. During the remaining IRB approval period, the investigator is authorized to continue the research. When the investigator complies, in writing, with all requirements as determined by the *Expedited reviewe*r, reapproval and full release will be granted.

   If the Investigator fails to respond to the IRB's continuing review request letter within the remaining IRB approval period, the protocol has, or will be, classified as administratively closed. If IRB approval expires, all research-related activities must immediately cease, unless an exception is granted by the IRB Chair in consideration of a written request. The IRB will be notified of all exceptions granted by the IRB Chair.

**I. Referred for full IRB review**

IRB members assigned to perform an *expedited review* can refer the protocol for review by the full IRB.

**J. Full IRB Review Procedure**

1. If the research initially required full IRB approval, the Annual Continuance Request Application must also be approved by the full IRB. Unless at the initial approval it was determined that the project involves no greater than minimal risk and no additional risks have been identified then the application for continuing review can be reviewed as expedited continuing.

2. Applications for continuing review are scheduled for full IRB consideration at a scheduled meeting, if quorum can be obtained. Each attending member will receive in advance all continuing review applications and associated consent/assent documents to be considered at the meeting and have access to the complete protocol. IRB members are asked to review, as necessary, the complete IRB protocol record.

3. The IRB will determine whether or not increased monitoring and/or more frequent continuing review is required.

4. IRB approval periods for protocols reviewed by the full board begin as of the date of initial or continuing review. Approval periods cannot exceed one year, which is defined as one year from the date of IRB review. IRB approval, therefore, expires one year later, or sooner if the IRB sets a more frequent continuing review date. For example, if the IRB reviewed a protocol on February 17, 2013, and set an approval period of one year, IRB approval would be valid until February 17, 2014. This means that IRB approval is in force until 11:59 pm February 16, 2014. As of midnight all research activity must cease unless IRB re-approval and full release has been granted.

**K. Full IRB Actions**

1. ***Re-approval and full release***
    a. No modifications or clarifications are required. All of the criteria for IRB approval specified in Health and Human Services regulations at 45 CFR §46.111 are satisfied. The investigator will be notified of the re-approval in writing and is authorized to continue the study.

2. ***Re-approval and full release (with minor clarifications)***

    Minor clarification(s) or information concerning the protocol is necessary for completion of the record. This action is only taken when the clarification(s) is (are) minor and does not impact protection of human subjects and/or the approvability of the consent document(s). The investigator will be notified of the re-approval in writing and asked to make the necessary modifications and return the materials before final approval of Continuance Request can be granted.

    Failure to respond to the IRB Continuance review clarification letter may result in the full IRB revoking approval of the study. In such a case, all research related activities must immediately cease, unless an extension is granted by the IRB Chair in consideration of a written request from the investigator. The IRB will be notified of all extensions granted by the IRB Chair.

The IRB Chair is empowered by the IRB to review the Investigator's response and grant re-approval and full release.

3. ***Conditional approval***, contingent upon IRB Chair acceptance of specific modifications/ clarifications

   This category is restricted to modifications/clarifications, which are not considered to be substantive in nature.

   The investigator will be notified in writing as to the nature of the required modifications/clarifications. During the remaining IRB approval period, the investigator is authorized to continue the research. When the investigator complies, in writing, with all requirements as determined by the IRB Chair, reapproval and full release will be granted.

   If the Investigator fails to respond to the IRB's continuance review letter within the remaining IRB approval period, the protocol has, or will be, classified as "administratively closed". If IRB approval expires, all research-related activities must immediately cease, unless an exception is granted by the IRB Chair in consideration of a written request. The IRB will be notified of all exceptions granted by the IRB Chair.

4. ***Conditional approval***, contingent upon full IRB re-review of specific modifications/clarifications.
   This category is restricted to modifications/clarifications, which are considered substantive in nature, but are not of sufficient magnitude to require a hold be placed on subject accrual. The Investigator will be notified in writing as to the nature of the required modifications/ clarifications. During the remaining IRB approval period, the investigator is authorized to continue the research. When the investigator complies, in writing, with all requirements as determined by the full IRB at a convened meeting, re approval and full release will be granted.

   If the Investigator fails to respond to the IRB's continuance review letter within the remaining IRB approval period, the protocol has, or will be, classified as suspended. If IRB approval expires, all research-related activities must immediately cease, unless an exception is granted by the IRB Chair in consideration of a written request. The IRB will be notified of all exceptions granted by the IRB Chair.

5. **Tabled with re-review by the full IRB**
   This action is taken when the IRB has identified significant concerns related to subject safety and/or conduct of the study. All research-related activities must immediately cease, unless an exception is granted by the IRB Chair in consideration of a written request. The IRB will be notified of all exceptions granted by the IRB Chair.

   The IRB must receive a satisfactory response from the investigator regarding any necessary modifications and/or clarifications of the protocol and/or consent document(s) within *thirty (30) business days*. Failure to respond to the IRB continuing review letter within the designated time period may result in termination of the study.

6. **Decline to Complete Review**
   This category is restricted to applications that are deficient and preclude the IRB from performing a substantive and meaningful review. The investigator will be instructed in writing to revise the application in accordance with IRB requirements. During the remaining IRB approval period, the investigator is authorized to continue the research.

   If the Investigator fails to respond within the remaining IRB approval period, the protocol will be classified as suspended, approval expired. If IRB approval expires, all research-related activities must immediately cease, unless an exception is granted by the IRB Chair in consideration of a written request. The IRB will be notified of all exceptions granted by the IRB Chair.

7. **Disapproved**
   The IRB has a serious concern regarding subject safety and/or compliance. The protocol will be suspended or possibly terminated. No new subjects can be accrued. All research-related activities must cease and the full IRB will make a determination if currently enrolled subjects may continue participation in the study.

**L. Final progress reports**

When a project is terminated or completed, the Investigator must immediately notify the IRB by completing the *Conclusion of Study Report* as the final progress report.

**M. Five-year re-application**

Continuation of projects beyond five (5) years (and every 5 years thereafter) requires submission of the Annual Continuance Request application, informed consent/assent document(s).

**N. Secondary Approval Process**.

"Secondary Approval" refers to studies which have already been subjected to review and approval by another qualified IRB, and in which limited study activity will occur at NMC, such as data collection through online or in-person surveys, questionnaires, education, or interactions with participants. Secondary approval requests must be submitted to the Chair of the IRB. Secondary approval may be provided by the IRB Chair or designated IRB member(s) and will depend on the nature of the activity at NMC.

The IRB Chair or designated IRB member(s) will review the following documentation submitted by the Investigator(s):

a. Copies of the original IRB application with all appendices (proposed study materials such as survey, recruitment letters, etc.) from the supervising IRB.
b. The proposed informed consent document. The informed consent document must clearly authorize the activity that will occur at NMC and must comply with usual IRB standards for informed consent, FERPA standards, and HIPAA authorization.
c. CITI or another official certification on Protection of Human subjects
d. Signed NMC Investigator Agreement form.

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

The Investigator(s) must agree to furnish the IRB Chair with any substantial follow-up information presented to or developed by the supervising IRB, and must agree to notify the IRB Chair immediately if the study is terminated, curtailed, or amended, or if any change in the Investigator's status occurs, such as the Investigator is terminated, curtailed, or amended by the supervising IRB.

The Investigator(s) must agree to appear before meetings of the IRB if requested, and furnish the IRB Chair or the IRB with such reports or additional information as are requested, from time to time. Upon receipt of all required information, the IRB Chair may accept the other IRB's review of the study, subject to any limitations he or she deems appropriate, or the IRB Chair may require full review and approval by the full IRB before any part of, or support for, the study proceeds at NMC. The IRB Chair shall report actions taken to the full IRB.

## Suspension and Termination

Suspension of IRB approval is a directive of the convened IRB or IRB Chair or IRB Chief Compliance Officer either to temporarily or permanently stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review. Termination of IRB approval is a directive of the convened IRB to stop permanently all activities in a previously approved research protocol.

Terminated protocols are considered closed and no longer require continuing review.

1. The IRB Chair may suspend research to ensure protection of the rights and welfare of subjects. Suspension directives made by the IRB Chair must be reported to and reviewed by the convened IRB. Research may only be terminated by the convened IRB. Terminations of protocols approved under expedited review must be made by the convened IRB.

2. When study approval is suspended or terminated by the convened IRB or an authorized individual, in addition to stopping all research activities, the convened IRB or individual ordering the suspension or termination will notify any subjects currently participating that the study has been suspended or terminated. The convened IRB or individual ordering the suspension or termination will consider whether procedures for withdrawal of enrolled subjects are necessary to protect the rights and welfare of subjects, such as: transferring subjects to another investigator; making arrangements for care or follow-up outside the research; allowing continuation of some research activities under the supervision of an independent monitor; or requiring or permitting follow-up of subjects for safety reasons.

3. If follow-up of subjects for safety reasons is permitted/required by the convened IRB or individual ordering the suspension or termination, the convened IRB or individual ordering the suspension or termination will require the subjects should be so informed and that any adverse events/outcomes be reported to the IRB and the sponsor.

4. It is the policy of the IRB that the following incidents will be promptly reported to OHRP and Department or Agency heads (if applicable) in accordance with Health and Human Services regulations at 45 CFR §46.108(a)(4) or to other federal agencies when the research is overseen by those agencies: 1) any unanticipated problem involving risk to the subject or others, 2) any serious noncompliance, 3) any continuing noncompliance, 4) any suspension or termination of IRB approval, and 5) any internal or external holds placed on IRB approved protocols (HRPP 14.002).

# INVESTIGATOR RESPONSIBILITIES

## Procedure for Submission

Before undertaking any research study, an Investigator shall submit a completed Application for IRB approval, which shall include any Consent or Assent forms, any forms/materials the Investigator will use, any data collection form that Investigator may use, and copies of letters of permission from agencies/data sources, if applicable.

The Application must be completed in advance of any research and submitted to the IRB Chair or IRB Manager. All accompanying documentation requested in the Application must be submitted to the above individuals and shall not be considered complete or reviewable until all required documentation is delivered to the IRB Chair or IRB Manager.

After the IRB Chair or IRB Manager has accepted the completed Research Application, and its supporting documentation, the IRB Chair, and if necessary, the IRB shall follow the procedures provided in the IRB Review Category provided herein.

The IRB shall ensure that all Investigators are familiar with the:

A. Belmont Report
   http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

B. 45 CFR 46 of the Code of Federal Regulations:
   http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

C. Nebraska Methodist College IRB Policy Manual

**External Constituents**

Investigators from outside of NMC that wish to carry out studies at NMC or with NMC faculty, staff, or students ("External Constituents") must submit an application to the IRB. External Constituents must obtain approval to perform a study from the Provost/VPAA if the study is to be performed on NMC students and faculty, and approval from the NMC President and CEO if the study is to be performed on NMC staff. External Constituents are required to follow the NMC IRB policies and procedures as outlined in this IRB Policy Manual. Any studies by External Constituents must be in alignment with the mission, vision, core values, and strategic priorities of NMC. Furthermore, prior to dissemination all results from studies by External Constituents must be reviewed by the IRB Chair. NMC faculty who are students at an external institution are considered External Constituents and must obtain IRB approval from the external institution prior to applying for IRB approval from NMC.

## Investigator Responsibilities, Standards and Corrective Action

**Responsibilities and Standards**

Investigators participating in research studies under the approval of NMC's Institutional Review Board are responsible to constantly meet the following standards. Failure to meet these standards could result in suspension or revocation of a study's approval, temporary or permanent revocation of an Investigator's individual authority, or other appropriate sanctions. The IRB Chair will monitor Investigator's compliance and report deficiencies to the IRB Administrator.

**A. Credentials**

1. Be specifically approved by the IRB to participate as a principal or secondary Investigator.

2. Notify NMC's IRB Chair of any significant changes in the Investigator's licensure, training or experience as related to the research study, authorization from the study sponsor or other change in the relationship with the sponsor, and any adverse actions by the Department of Health and Human Services.

**B. IRB – Related Training**

1. Review, understand and abide by all terms and provisions of this Policy Manual.

2. Complete the current on-line IRB training course, Collaborative Institutional Training Initiative (CITI), approved by the IRB and provide documentation of successful completion to the IRB Manager or IRB Chair prior to the Investigator's submission of his or her first IRB Application with the NMC IRB. The costs of registration will be paid by NMC. Investigators who have completed IRB training at a different institution can satisfy this requirement by providing documentation of successful completion of CITI training course to the IRB Manager or IRB Chair.

3. Every two (2) to three (3) years following completion of the initial on-line IRB training, Investigators will be expected to complete a supplemental on-line IRB training course and provide documentation of successful completion and re-certification to the IRB Manager or IRB Chair, if they have a continuing research study that spans more than the two (2) to three (3) years following the initial on-line IRB training.

4. Cooperate in any other reasonable request by the NMC IRB, for continued education in connection with IRB-related and human research-related issues.

**C. Paperwork / Reporting**

1. File all required reports with the IRB on a timely and complete basis.

2. Complete on a timely basis all required reports to regulating authorities.

3. Immediately notify the IRB, through the IRB Chair, of any temporary or permanent suspension or closure of the study; 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.

4. Obtain prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and documentation, except those necessary to eliminate apparent immediate hazards to subjects.

5. Provide the IRB with prompt reports of any unanticipated problems involving risks to subjects or others as set forth in this manual.

6. Provide the IRB with prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB.

**D. Informed Consent**

1. Unless waived, obtain full informed consent from each subject participating in the research study or legally authorized representative, utilizing a consent document specifically approved for the study by the IRB.

2. Notify study subjects of any material new information, which might affect the subject's willingness to participate in the study.

3. Keep copies of all signed informed consent documents, and other study related documents, on file for the entire duration of the study, and at least three (3) years following completion of the study.

4. Provide current copies of the informed consent document 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.

**E. Financial Interests**

1. Assure that he or she has no financial interest, which will influence the decision to enroll a patient as a study subject, or influence study procedures or outcomes.

2. Fully disclose to the IRB, on the initial application and subsequently at the time of annual review or if there is a substantial change, all payments sources to the investigator participating in the research; and any significant financial interest the Investigator has in the research study. The NMC IRB has established the following definitions:

   "Significant financial interests" in research studies include the following interests of the Investigator and his or her spouse or children, or of any foundation, corporation, LLC, partnership or other entity in which the Investigator or his/her spouse or children exercise authority as an owner of 5% or more, a trustee, a director, a manager, or a compensated employee:

   a. Consulting fees, honoraria, gifts or other emoluments, or "in kind" compensation, received directly or indirectly from the study Sponsor or another person or company with a significant financial interest in the research, whether for consulting, lecturing, travel, service on an advisory board, 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.

b. Equity interests, including stock options, of any amount in the Sponsor or another entity with a significant financial interest in the research, 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.
c. Royalty income or the right to receive future royalties under a patent, license or copyright, where the research is directly related to the licensed technology or work.
d. Any non-royalty payments or entitlements to payments in connection with the research that are not directly related to the reasonable costs of the research. This includes any bonus or milestone payments to the investigators in excess of reasonable costs incurred.
e. Service as an officer, director or in any other managerial or fiduciary role for the study Sponsor, whether or not remuneration is received for such service.

Payments that are directly related to reasonable costs incurred in the conduct of the research are excluded.

3. Cooperate with any directive of the IRB to address significant financial interests. The IRB may, in its discretion, request additional detailed information at any time; conclude that under the circumstances, the financial interest does or does not pose any additional risk to the welfare of the subjects or the integrity of the research; deny or grant approval to participate in the research while the financial interest exists; impose periodic monitoring and reporting requirements as a condition of approval; require disclosure of the financial interest in the consent document; or take other action appropriate under the circumstances, in its discretion.

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

5. Not accept payments for subject enrollment or for referral of subjects to the study, unless such payments are reasonably related to actual costs incurred.

**F. Audits and Investigations**

1. Cooperate fully, at all times upon request of the IRB, in any audits or investigations by or on behalf of the IRB, including but not limited to audits of informed consent documentation.

2. Cooperate fully in any audits or investigations by the study Sponsor or HHS, and notify the IRB promptly in the event any such audit or investigation is initiated.

**G. Investigator Agreement**

Execute and return the IRB Individual Investigator Agreement.

**H. Non-compliance Policy**

Failure (intentional or unintentional) to comply with the requirements or determinations of the IRB, or policies regarding research involving human subject will result in suspension or termination of IRB approval of research. Noncompliance can result from action or omission.

## I. MODIFICATIONS.

1. **Modification**. A protocol modification involves any proposed changes to the approved research protocol that impact the study design, objectives, methodology, participant recruitment, or other key elements. Modifications can be substantial or minor, ranging from changes in study procedures to adjustments in the inclusion/exclusion criteria or sample size. Unlike deviations, protocol modifications require prior approval from the IRB before implementation. Investigators must submit a formal amendment to the IRB, outlining the proposed changes and providing justification.

2. **Request for Modification**. The IRB must review and Approve any modification to a study, including, but limited to, Modifications to the Protocol, Informed Consent Form, or materials distributed to Subjects.

3. **Procedures for Modifications**. Investigators shall submit a completed Request for Modification Form to the IRB Chair, together with any additional information as requested by the IRB, prior to the implementation of the 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 that 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 IRB Chair may approve the Modification via Expedited Review.

## J. PROTOCOL DEVIATION.

1. **Protocol Deviations**. A protocol deviation occurs when there is an unplanned or unintentional diversion from, or non-compliance with, the approved research protocol without prior approval from the IRB. Deviations can be minor or major and may involve changes in the study procedures, data collection methods, or other aspects outlined in the approved protocol. Investigators are required to report protocol deviations to the IRB. The IRB must Approve any deviation from the procedures set forth in an approved protocol.

2. **Procedures for Deviations**. The Investigators shall submit Deviations to the IRB Chair using the Protocol Deviation Report Form, together with any additional information as requested by the IRB.

   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.

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

## Unanticipated Problems Involving Risk and Adverse Events

The purpose of this section is to describe the procedure to ensure prompt reporting to the IRB, appropriate institutional officials, sponsor, coordinating center, and the appropriate regulatory agencies of unanticipated problems involving risks to subjects or others.

**A. Definitions**

1. **Unanticipated Problems Involving Risk to Subjects or Others**. This term is defined as an adverse event that is (1) unexpected, (2) serious, and (3) related or possibly related to participation in the research. Unanticipated problems also include unexpected adverse events, regardless of severity, that the IRB determines represent risk to subjects or others. Unanticipated problems also include events that are not categorized as adverse events and are not directly related to an individual subject's participation in a study, but represent risk to subjects or others.

   ***Example: Events that could lead to a breach of confidentiality or privacy provisions such as the unanticipated loss or theft of files or that in any way might subject the research subject to a higher degree of risk than anticipated in the research protocol.***

2. **Adverse Event (AE)**. This term is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.

3. **Serious Adverse Event (SAE).** This term is defined as death; a life-threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

4. **Unexpected Adverse Event (UAE).** This term is defined as any adverse event and/or reaction, the specificity or severity of which is not consistent with the informed consent, current investigator brochure or product labeling. Further, it is not consistent with the risk information described in the general investigational plan or proposal.

5. **Related.** An event is "related" if it is likely to have been caused by the research procedures**.**

6. **Substantive Action.** An action taken by an IRB that materially alters the substance and meaning of a protocol, informed consent form or process, or investigator status, including, but not limited to, restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the AE in research.

7. **Unexpected Death.** The death of a research subject in which a high risk of death is not projected, as indicated by the written protocol, informed consent form, or sponsor brochure. This definition does not include deaths associated with a terminal condition unless the research intervention clearly hastened the subject's death. A subject's death that is determined to be clearly not

associated with the research is also not an "unexpected death" for purposes of the reporting requirements of these procedures.

**B. Guidelines for Reporting Unanticipated Risks and Adverse Events.**

It is the IRB's policy to comply with Health and Human Services regulations at 45 CFR §46. 108(a)(4) to have policies and procedures that ensure reporting of all unanticipated problems involving risk to subjects or others to the IRB, regulatory agencies, and institutional officials.

**The following problems must be reported immediately to the IRB within 48 hours using the *Adverse Event Report Form*:**

1. Any physical or psychological harm experienced by a subject, which in the opinion of the principal investigator, is both unexpected and related.

    a. Harm is "unexpected" when its specificity and severity are not accurately reflected in the consent document.

    b. Harm is "related to the research procedures" if in the opinion of the principal investigator, it is more likely than not to be caused by the research procedures or if it is more likely than not the event affects the rights and welfare of current subjects.

2. Information that indicates a change to the risks or potential benefits of the research. For example:

    a. An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits might be different from those initially presented to the IRB.

    b. A paper is published from another study that shows that the risks or potential benefits of your research might be different from those initially presented to the IRB.

3. A breach of confidentiality.

4. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research subject

5. Incarceration of a subject in a protocol not approved to enroll prisoners.

6. An event that requires reporting to the sponsor.

7. Sponsor imposed suspension.

8. Complaint of a subject.

9. Protocol deviation.

**C. Guidelines for IRB Review of Unanticipated Risks and Adverse Events**

1. The IRB Chair reviews problem reports and determines whether each is an unanticipated problem involving risks to subjects or others. If the report is an unanticipated problem involving risks to subjects and others, it is referred to the convened IRB for review. The IRB Chair also considers whether each report involves noncompliance. If so, the noncompliance policy is followed. If the IRB Chair determines that the report is neither an unanticipated problem involving risks to subjects or others nor noncompliance, it is filed and no further action is taken.

2. The IRB Chair will take all actions necessary to protect human subjects including suspension or termination of the study. Investigators may also make changes to the research without prior approval by the IRB when necessary to eliminate apparent immediate hazards.

3. If referred for full IRB review, two (2) IRB reviewers are assigned to review the Adverse Event Report Form. These members are provided and expected to review, in depth, copies of:
   a. The Report of Unanticipated Problem Involving Risk and all submitted supporting materials.
   b. The current consent document.
   c. The protocol application.
   d. The industry protocol (if one exists).
   e. The investigator's brochure (if one exists).

4. All IRB members are provided and are expected to review, be familiar with, and be prepared to discuss copies of:
   a. The Report of Unanticipated Problem(s) or Adverse Event(s) Involving Risk and all submitted supporting materials.
   b. The current consent document.

5. If the IRB determines the problem is not an unanticipated problem involving risks to subjects or others, the IRB determination overrules the determination of the IRB Chair, and no further action is taken. The IRB determination of whether the problem is an unanticipated problem involving risks to subjects or others is documented in the minutes.

# Informed Consent and Privacy

**Informed Consent**

The most fundamental condition 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 will expose the Investigator to a claim of medical malpractice (and in some settings, possibly to a claim of assault and battery). In the research arena, however, the IRB is also charged with oversight responsibility for the consent process, which is exercised by (i) approving the informed consent documents to be used, (ii) obtaining the Investigator's certification that informed consent will be obtained and documented in every case, and (iii) reserving the right to audit the consent process and documentation in any case. In addition, for studies involving federal funding or FDA drugs or devices, federal regulations define the necessary elements of informed consent for human research, and require a much more extensive consent document than typically used for non-research medicine and surgery. Consent documents that meet the federal regulatory requirements are generally expected by the IRB, even for studies that are not subject to the regulations.

**A. The Process of Informed Consent**

The Investigator has a legal and an ethical obligation to ensure that the prospective subject has sufficient knowledge and comprehension of the elements of informed consent. This means the prospective subject must be able to make an informed and enlightened decision to participate in research. Informed consent should be documented with a complete consent document written in clear, understandable language at the appropriate educational level ($5^{th}$-6th grade level is recommended as a benchmark). Informed consent must be obtained by the Investigator. If the circumstances warrant a need to minimize the possibility of coercion or undue influence (e.g. investigator is one who may teach or assign a grade to a current or future student), a representative for the investigator may obtain informed consent.

The consent document, however, does not by itself constitute informed consent. Rather, the informed consent document should serve as a guide by which the Investigator obtains informed consent with the prospective subject. During the process of informed consent, each element of consent should be carefully, patiently and simply explained to the prospective subject. In addition, the investigator 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, nurses and other ancillary personnel. Although the investigator may facilitate all or part of the informed consent disclosure process, it must, however, be remembered that the Investigator bears full and ultimate responsibility for obtaining valid informed consent from the subject.

During the consent process, the Investigator should explain to the subject his or her rights as a research subject. The explanation of a research subject's rights is considered an adjunct to informed consent and serves to demonstrate a commitment to the conduct of human subject research with the highest integrity and skill possible. The Investigator should be careful to explain to the subject that the protocol is a research protocol involving experimental treatment; that there is no assurance (or where appropriate, no intention) of therapeutic benefit to the subject, understanding that prospective

subjects may overestimate the potential benefit unless clearly told otherwise; and that the subject has a choice to consent or not consent.

**B. Documentation of Informed Consent**

1. **Informed Consent Document**. After the Investigator has determined that the prospective subject (or legally authorized representative) has sufficient knowledge and comprehension of each element of consent, the subject (or legally authorized representative) should read (or have read to him or her) and voluntarily sign and date (including in an electronic format) the informed consent document. The Investigator or authorized staff should sign and date (including in an electronic format) the consent document. Authorized staff may sign a consent document for a given research protocol only if they possess sufficient information about the research protocol and are authorized by the Investigator to obtain informed consent. A written copy should be given to the person signing the informed consent form.

   The informed consent form may be in either of the following:

   a. A written informed consent form that meets the requirements of 45 CFR §46.116. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternately, this form may be read to the subject or the subject's legally authorized representative.

   b. A short form written informed consent form stating the elements of informed consent required by 45 CFR §46.116 have been presented to orally to the subject or the subject's legally authorized representative, and that the key information required by §46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The investigator will provide a written summary of what is to be said to the subject or the subject's legally authorized representative to the IRB for approval. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.

   When geographic distance between the subject and the research site are significant, telephone or electronic consent may be used, and written consent may be obtained using a mailed, faxed, or scanned and e-mailed consent document. In such cases of telephone consent, the subject should be sent a copy of the entire consent document prior to the telephone discussion so that he or she has the opportunity to review it in advance. Following the telephone 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.

2. **Witnesses/Capacity of Subject**. Informed consent documents are only required to be witnessed in the event that the document must be read to the subject or to the subject's legally authorized representative or in the event that the subject's mental capacity is limited and/or transitory. In such a case, the witness must be present during the entire presentation of the informed consent document and will sign after the subject or legally authorized representative has signed as

verification that the entire consent document was read and the consent was signed as a voluntary act. When the subject's mental capacity is transitory, it is recommended that the individual making the informed consent disclosures ask the subject preliminary questions to establish that the subject is oriented and capable of appreciating the effect of his or her actions before proceeding with the informed consent process. If the subject does not appear to have sufficient capacity to comprehend the disclosures or appreciate the effect of his or her actions, it is advisable to obtain consent from a legally authorized representative rather than the subject him or herself. In the absence of an attorney-in-fact under a health care power of attorney or a court-appointed guardian, close relatives may give consent. Consult legal counsel as necessary to determine who may act as a legally authorized representative for an incapacitated subject.

3. **Copy to Subject.** A copy of the informed consent document shall be given to the subject or the subject's legally authorized representative).

**C. Informed Consent Document - General Recommendations**

1. **Identification.** The consent document should clearly identify itself as consent for a research study. It is permissible to identify on the document, the fact that it was approved by the NMC IRB and the approval date(s). The individual being asked to participate should be referred to as the "subject," not as the "patient" or "participant" or by any other term that lessens the message that the consent is for experimental research.

2. **Style.** It is recommended that the informed consent document 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 Investigator believes there is a choice to be made by the prospective subject; use of the first person may be interpreted as presumption of subject consent before consent has been legally obtained.

3. **Readability.** The most common consent document deficiency is that the consent is too difficult to read and understand. A prospective subject's ability to understand the elements of informed consent is a function of intelligence, education, maturity, and language skills. It is, therefore, necessary to adapt the language level of the consent document to fit the subject's capabilities. The informed consent document must be written in simple enough language so that it is readily understood by the least educated, least sophisticated of the subjects to be enrolled. It is recommended that the language consist of short, concise sentences arranged in relatively short, simple paragraphs. Headings and subheadings should be used to increase readability and comprehension. It should be remembered that terms that are commonly used by members of a profession become a part of the professional's language; many people outside that profession, however, do not understand the language. Common words in medicine, such as "catheter, intravenous (let alone IV), prognosis, symptomatology, randomly assigned, efficacy, placebo, blinded," etc., are not understood by many laypersons. If there is any doubt that a term may not be understood, a simpler term should be used or a definition should be added, e.g., ". . . intravenous (given directly into a vein by way of a needle)."
   ***Note: The NMC IRB is recommending that all informed consent forms be written at the 5$^{th}$ to 6$^{th}$ grade reading level for subjects recruited from the general population*.**

4. **Exculpatory Language.** The informed consent document must not contain any exculpatory language through which the subject or the subject's representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the Investigator, the sponsor, the institution or its agents from liability for negligence.

5. **Foreign Language Consent Documents.** To the extent required by the needs of subject populations, the Investigator will arrange for translations or interpreters to assist non-English speaking subjects with the informed consent process.

**D. Required Elements of Informed Consent**

Federal regulations define the following elements of a complete informed consent document. These elements should be presented in the same sequence as they are described below.

1. **Title of the Research 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, detailed protocol, and consent document.

2. **Invitation.** The consent document should begin with a clear statement that the study involves research and an invitation to participate in a research study. The document 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 document.

3. **Purpose.** This section of the consent document is often considered the most important. It should give the subject a sound context in which to consider the risks, benefits, and alternatives of the study. This section should be very carefully written, and should contain a clear, understandable and accurate statement of the purpose and objectives of the research, with the expected duration of the subject's participation in the study. This 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.

4. **Study Procedures.** This section of the consent document explains the study procedures and should include the following:
   a. A simplified description of the study design (*e.g.*, longitudinal, single-blind, double-blind), 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, subjects must be made aware of all the possible interventions and the method of assignment.
   b. A sequential description of each procedure to be applied to human 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 projects, it may be appropriate to identify the individual(s) who will perform the procedures and/or interact with the subject.

c. 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.
d. A statement concerning any medications, therapeutic regimens, foods, or other substances that are contraindicated or disallowed either before or during participation in the study.
e. The explanation of procedures section should not contain detailed instructions to the subject which do not impact significantly on the consent process. Detailed instructions should be placed on a separate handout.

5. **Possible Risks and Discomforts.** The consent document should fully disclose any reasonably foreseeable risks which 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. From both an ethical and legal perspective, this section of the consent document is extremely important.

   Both immediate and latent risks of each procedure or intervention carried out for research purposes should be clearly described in this section of the consent document. 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. 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" should be defined in language that a research subject can easily understand.

   In most therapeutic research projects, the consent document should also state that there may be risks associated with the research that are currently unknown.

6. **Possible Benefits.** This section of the consent document should 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 nontherapeutic research, this should be stated and should be explained orally before the subject's consent is accepted.

   The Benefits section of the consent document should **not** describe financial compensation or other forms of remuneration. Compensation should be described only under element #10.

All research must obviously have some underlying potential benefit to society (e.g., advancement of knowledge, health benefit to others). Potential societal benefits may, therefore, be described in this section of the consent document.

7. **Alternatives.** The consent document should 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 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.

8. **Confidentiality.** This section of the consent document should 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 authorization. However, the subject should be advised that information regarding the subject may be sent to or accessed by representatives of the Investigators, NMC, the NMC IRB, and/or HHS.

   The consent document should 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.

   Pursuant to the privacy regulations of HIPAA, a separate Authorization for Disclosure form such as the sample in the following section should also be executed. Alternatively, the required elements of a HIPAA authorization can be incorporated into the informed consent document.

9. **For research involving more than minimal risk,** this next section should include an explanation as to whether there is any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

   a. **Compensation for Participating.** Any compensation for participation should be clearly stated in the consent document. 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. If no compensation will be paid, this 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.

   b. **Medical Treatment**. If the investigator or a commercial sponsor has agreed to provide any medical treatments to research subjects, the informed consent should state as clearly and carefully as possible, a description of the medical treatment that will be provided. This includes the location where additional information about the medical treatment may be obtained by the subject.

10. **Rights as a Research Subject.** This section of the consent document should contain an explanation of the research subjects' rights and whom to contact for answers to pertinent questions about the research.
    a. The consent should contain essentially the following language:

    *If you have any questions about your rights as a research subject, you may contact Nebraska Methodist College's Institutional Review Board, a group of people who are responsible to protect the rights of research subjects, by calling 402-354-7031 (ask to speak to the IRB Chair).*

    b. The consent should contain the investigator's name and contact information, including telephone number and email address.

11. **Injury and Emergency.** The consent document should contain information on whom to contact in the event of a research-related injury. Advise the subject, in simple terms, what to do in case of an emergency or research-related injury. Typically, the subject is advised:
    a. Whom to contact (usually the Investigators) with names and phone numbers.
    b. That emergency care will be available at the subject's expense at NMH or another facility of his/her choice.
    c. That no additional compensation will be provided.
    d. That signing the consent document does not mean that the subject is waiving any legal rights he or she may have.

12. **Voluntary Participation.** This section of the consent document should contain essentially the following language:

    *It is your choice to be a part of this research study. It is your choice if you want to take part in the research study or not. You can decide not to be a part of this study. You may stop the study at any time without any loss of benefits to which you may have due. If any new information develops during the course of this study that may affect your decision to continue being a part of the study, you will be told.*

13. **Identifiable private information or identifiable biospecimens**. For any study that involves the collection of identifiable private information or identifiable biospecimens, one of the following statements should be included in the consent document:

    a. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or legally authorized representative.

    b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research.

14. **Consent (Assent) Statement.** This section of the consent document should contain essentially the following language:

    You are making a choice to be a part in this research by your own free will. Signing this form means that information given to you has been fully explained, all your questions have been answered, and that you understand the information given to you. If you think of any more questions during the study, you should contact the person doing the research. You will be given a copy of this consent document.

15. **Signature Blocks.** The signature blocks should be as follows for documentation of any consent related to the study and for authorizing disclosure of protected health information (HIPAA Authorization):

| | | |
|---|---|---|
| Date | Time | Subject's Signature or<br>Signature of Subjects Personal Representative |
| Authority of Personal Representative if signing on behalf of subject | | Printed Name of Subject or<br>Subject's Personal Representative |
| Date | Time | Signature of Person Conducting Informed Consent Discussion |
| | | Printed Name of Person Conducting Informed Consent Discussion |

    In appropriate cases, the consent document should advise the subject that the Investigator has a financial interest in the study, and explain that interest in reasonable detail. The IRB may require such disclosure in any case, and will require it if the IRB determines that the Investigator's financial interest is substantial.

16. **Investigators.** At the end of the consent document, the names, addresses and home telephone numbers of the Investigators should be listed (unless listed earlier in the document)

**E. Additional Elements of informed Consent**

Federal regulations define additional elements of information that may need to be provided to each subject or legally authorized representative in a complete informed consent document. Investigators shall provide one or more of the following elements, when appropriate:

1. **Pregnant women & fetus risk.** This section provides a statement that a particular treatment or procedure may involve risk to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable. Research also will often pose risks to unborn babies. Studies shall not be performed on pregnant individuals unless further conditions are met. The IRB recommends the following specific text to address this risk, with modifications as appropriate to a specific study:

   Because the drugs in this study can affect an unborn baby, you should not become pregnant while you are participating in this study. You should not nurse your baby while in this study. If you are a woman of childbearing age and have not been surgically sterilized (tubal ligation, hysterectomy or oophorectomy), you may be required to have a negative serum pregnancy test before enrolling in this study, as well as a negative urine pregnancy test. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while in this study, you must tell your study doctor immediately.

   If you are a man of reproductive potential, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your study doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anybody to become pregnant after starting in this study, you must tell your study doctor immediately.

2. **Termination of Participation**. This section of the consent document provides a statement providing anticipated circumstances under which the subject's participation may be terminated without regard to the subject's or legally authorized representative's consent.

3. **Costs/Financial Obligations.** This section of the consent document should 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 third party payor.

4. **Consequences of Subject Withdrawal**. This section of the consent document provides a statement with the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5. **New Findings affecting Participation.** This section of the consent document provides a statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.

6. **Number of Subjects in Study**. This section of the consent document provides a statement with the approximate number of subjects involved in the study.

7. **Biospecimens used for Commercial Profit.** This section of the consent document provides a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit.

8. **Disclosure of Research Results.** This section of the consent document provides a statement regarding whether clinically relevant research results, will be disclosed to subjects, and if so, under what conditions.

9. **Genome Sequencing of Biospecimens**. This section of the consent document is for research involving biospecimens and includes providing a statement regarding whether research (if known) might include whole genome sequencing.

**F. Elements of Broad Consent**

Federal Regulations defines elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or for nonresearch purposes) is permitted as an alternative to the informed consent requirements in 45 CFR §46.116(b)and (c). Examples of studies using identifiable private information include chart reviews, student grades, private interviews, or surveys of opinions and attitudes. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

1. This section of the broad consent document shall include the following elements required in an informed consent document: (1) a description of reasonable foreseeable risks or discomforts, (2) a description of any benefits that may be reasonably expected, (3) a statement describing the extent to which confidentiality will be maintained, (4) a statement that participation is voluntary, refusal to participate involves no penalty or loss of benefits, and subject may withdraw at any time without penalty or loss of benefits, and when appropriate, (5) an explanation of who to contact for answers to questions about the research and the research subject's rights, (6) one of the statements about any research that involves the collection of identifiable private information or identifiable biospecimens.

2. This section of the broad consent document provides a general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information, such that a reasonable person would expect that the broad consent would permit the types of research conducted.

3. This section of the broad consent document provides a description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens.

4. This section of the broad consent document provides a description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite).

5. Unless the subject or legally authorized representative will be provided details about any specific research studies, this section of the broad consent provides a statement that the subject or legally authorized representative will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of these specific research studies.

6. Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, this section of the broad consent provides a statement that such results may not be disclosed to the subject.

7. This section of the broad consent document provides an explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and to whom to contact in the event of a research related harm.

## G. Consent/Assent Procedures for Research Subjects Who Are Minors

Generally, minors lack legal capacity to consent on their own behalf. The consent of their parent(s) or a legal guardian is therefore required before they are permitted to participate in research projects. In the state of Nebraska, a minor attains majority at age 19 or upon marriage. Pregnancy does not, in itself, confer majority status. A minor may, however, with IRB approval, legally consent on his/her own behalf (as a mature minor) if the research involves a treatment for which a minor's consent is permissible under applicable law (e.g., use of contraceptives or treatment of venereal disease). If a subject under the age of 19 is legally emancipated by marriage or life circumstances as defined by the law of the state in which the research is being conducted, he/she may consent to participate in research.

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. In cases where the research involves a greater than minimal risk to the child and no prospect of direct benefit to the individual child but is likely to yield generalizable knowledge about the subject's disorder or condition, consent of both parents must be obtained unless 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 child.

In addition to obtaining the parent's/legal guardian's **consent**, the Investigator must also solicit **assent** of minor subjects age 7 and older, unless the subject displays intellectual or emotional development below that of the average 7-year-old child. Obtaining assent shows respect for a child's developing

autonomy. In most circumstances, a child's deliberate objection should be regarded as a veto to his or her involvement in the research. However, parents or guardians may, with IRB and physician approval, override a young child's objections to interventions that hold the prospect of direct benefit to the child. The Child Assent Form must be **brief** and contain **extremely simple** language arranged in numbered paragraphs. Only elements 1-6 and the concluding assent statement must be included.

**H. Waiver or Alteration of Consent or Authorization**

Under certain circumstances, the IRB may grant a waiver of the requirement for documentation of informed consent, alter those provisions which must be included in an informed consent, or grant a waiver of the HIPAA requirement of authorization for use or disclosure of protected health information (PHI) in connection with a human research study**.** A *Waiver of Documentation of Informed Consent* form must be submitted with to the IRB with the IRB application. The IRB may approve a consent that omits some, or alters some or all, of the required and additional elements of informed consent provided the IRB satisfies the requirements for waiver or alteration. An IRB may not omit or alter any of the general requirements described in 45 CFR §46.116(a). If a broad consent procedure is used, an IRB may not omit or alter any of the elements required.

**Please note that for exempt research with some kind of interaction with the subject, the investigator may request a waiver of documentation of Informed consent (if requirements are met), but the investigator must provide required elements of informed consent as a *Consent Cover Letter* to the subject or subject's legally authorized representative. Exempt research, in which there is no interaction with subjects (*e.g.*, medical records), does not require a waiver of informed consent or documentation of informed consent from the IRB. Only the IRB, acting as a privacy board, can grant a partial or full waiver of HIPAA patient authorization.**

1. **Requirements for Waiver and Alteration of Informed Consent.** The IRB must find that:
   a. The research involves no more than minimal risk to the subjects.
   b. The research could not practicably be carried out without the waiver or alteration.
   c. If the research contains identifiable private information or identifiable biospecimens, the research could not 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.
   e. Whenever appropriate, the subjects or legally authorized representative will be provided with additional pertinent information after participation.

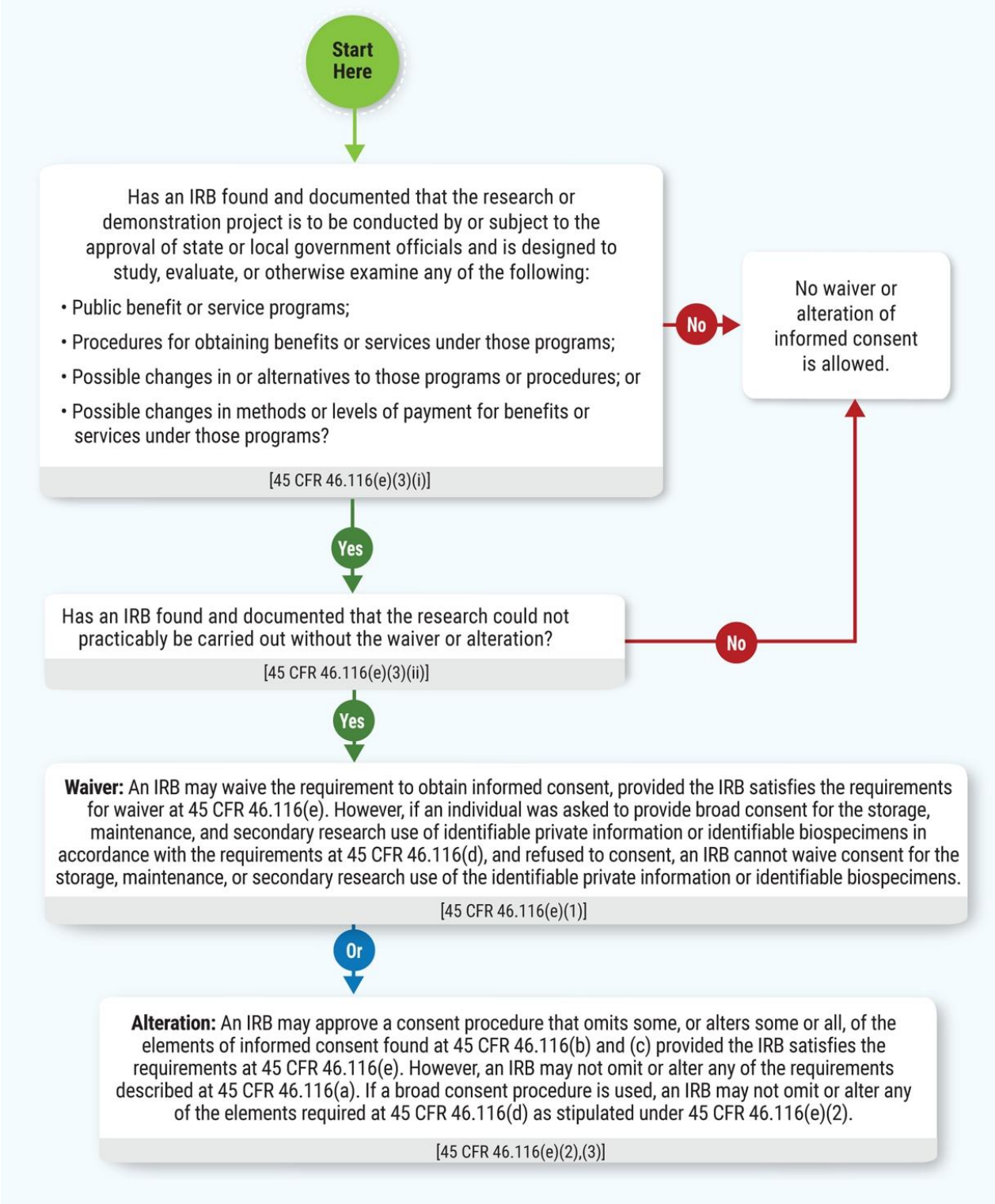
2. **Requirements for Waiver or Alteration of Consent in Research involving Public Benefit and Service Programs.** An IRB may waive the required and additional elements of informed consent informed consent for research involving public benefit and service programs conducted by or subject to the approval of state and local officials provided the IRB satisfies the requirements for waiver. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens and refuse to consent, an IRB cannot waive consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens. The IRB must find and document that:

a. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and designed to study evaluate, or otherwise examine: (1) public benefit or service programs, (2) procedures for obtaining benefits or services under those programs, (3) possible changes in or alternatives to those programs or procedures, (4) possible changes in methods or levels of payment for benefits or services under those programs.
b. The research could not practically be carried out without the waiver or alteration.

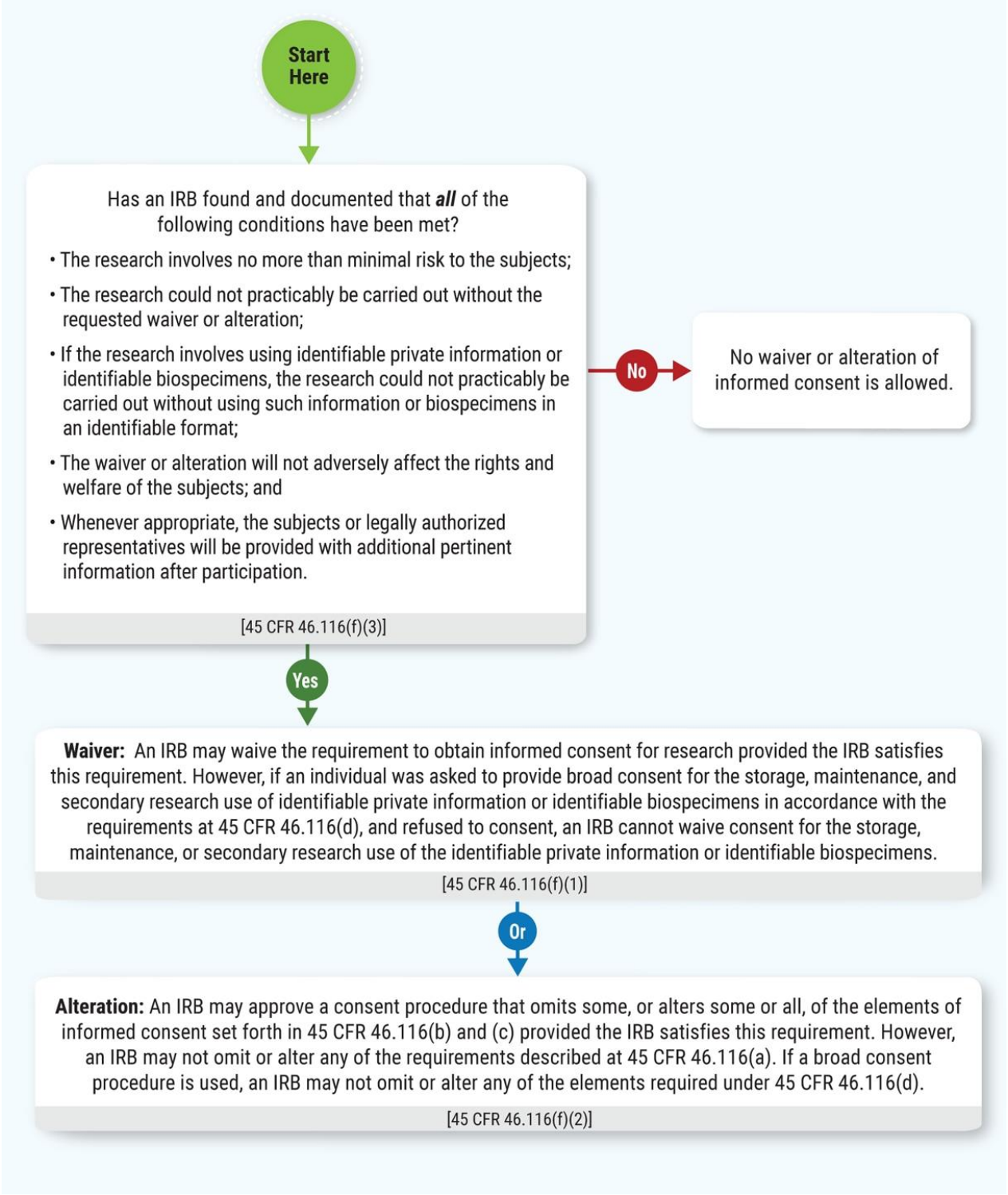
3. **Requirements for Waiver of HIPAA Authorization.** The IRB must find that:
   a. The study will involve no more than minimal risk to the privacy of individuals, including each of the following:
      i. There is an adequate plan to protect individual identifiers from use and disclosure.
      ii. There is an adequate plan to destroy individual identifiers at the earliest opportunity consistent with the conduct of the research, except when there is a health or research justification for retaining the identifiers or retention is required by law.
      iii. PHI will not be reused or disclosed to anyone else except as required by law, or for authorized research oversight, or for other research for which use/disclosure would be permitted under HIPAA.
   b. The research could not practicably be conducted without the waiver of individual authorization.

**See CHARTS 12 & 13 for analysis of potential waivers of informed consent.**

***Chart 12: Waiver or Alteration of Informed Consent in Research Involving Public Benefit and Service Programs Conducted by or Subject to the Approval of State or Local Government Officials (45 CFR 46.116(e))***



## *Chart 13: When Can Informed Consent Be Waived or Altered Under 45 CFR 46.116(f)?*



## I. Other HIPAA Exceptions

HIPAA regulations permit the use of protected health information (PHI) for research without the subject's Authorization or an IRB waiver in three instances: (a) within a "limited data set" as defined in the regulations, (b) for certain limited activities preparatory to research, or (c) for NMC research on decedents' information. Researchers planning to use PHI at NMC for any of these purposes without individual authorization should first contact NMC's Privacy Officer for advice and approval, and document that advice and approval when submitting the Request for Review or Request for Waiver to the IRB.

# The Belmont Report

# The Belmont Report

## 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**

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**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, there-by 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.

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

*Members of the Commission*

Kenneth John Ryan, M.D., Chair, Chief of Staff, Boston Hospital for Women.
Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.
Robert E. Cooke, M.D., President, Medical College of Pennsylvania.
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***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 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 well-being 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.

Federal law only mandates review and approval by an institutional review board, where both of the following criteria are met:

1. There is "human subject research" being conducted; and

2. The research is either:

1. Conducted or supported, in whole or in part, by the United States Department of Health & Human Services or another federal agency; or

2. Conducted for the purpose of obtaining approval by the FDA for commercial marketing (i.e., new labeling).

If covered under paragraph (a), then IRB review is required under the federal "common rule" at 45 C.F.R. Part 46. If covered under paragraph (b), then IRB review is required by regulations of the Food & Drug Administration at 21 C.F.R. Parts 50 and 56. The federal common rule and the FDA regulations are parallel, but not identical in all circumstances.

Generally speaking, "human subject research" is defined as a *systematic investigation designed to develop or contribute to generalizable knowledge,* where the investigation involves obtaining information about living individuals, either through intervention or interaction with the individuals, or through the use of individually identifiable and private information. Use of a drug or device "off label" on a patient-by- patient basis, where there is no element of data gathering and reporting for the purpose of contributing to generalizable knowledge, does not meet the definition of human subject research. 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, subject only to their 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 NMH policies or protocols. However, even if a drug or device is being used off-label on a patient-by-patient basis, if the physicians making such a use are gathering information for the purpose of later contributing to generalizable knowledge (through publication or through the provision of support for an expanded FDA marketing approval for the drug or device), then human subject research and IRB review will be implicated.

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**Part 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.

(2) ***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.

(3) ***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.

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**Part 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 disabled 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 entitle.

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.

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1. 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.

2. 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.

3. 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.