The Nebraska Methodist Hospital
Institutional Review Board

Handbook
for
IRB Members
And
Investigators

Guidelines for the
Protection of Human Research Subjects

2017
(Revisions Approved March 27, 2017)

Directory Information

Institutional Review Board	**The Nebraska Methodist Hospital** **Institutional Review Board** **8303 Dodge Street** **Omaha, Nebraska 68114** **402.354.4035**
IRB Chairperson	**William Lydiatt, M.D.** **The Nebraska Methodist Hospital** **8303 Dodge Street** **Omaha, Nebraska 68114** **402.354.4448** **William.Lydiatt@nmhs.org**
IRB Vice Chairperson	
IRB Manager	**Kristi Dziatkowski** **The Nebraska Methodist Hospital** **8303 Dodge Street** **Omaha, Nebraska 68114** **402.354.4036** **kristi.dziatkowski@nmhs.org**
IRB Legal Counsel	**Michael W. Chase** **Baird Holm LLP** **1700 Farnam Street** **1500 Woodmen Tower** **Omaha, Nebraska 68102-2068** **402-636-8326** **mchase@bairdholm.com**
IRB Registration #	**Nebraska Methodist Hospital IRB #1** **IRB 00002030** **Parent Organization Nebraska Methodist Hospital** **IORG 0001573**
IRB Federal-Wide Assurance #	**FWA0000337**

Page

Page

Page

Page

Page

I.
INTRODUCTION

Medical 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, pharmaceutical companies, device manufacturers, physicians and other researchers. The U.S. Food and Drug Administration (FDA) requires extensive research studies as a pre-condition to the marketing of most new drugs and devices, and the U.S. Department of Health and Human Services (HHS) actively supports and regulates numerous research projects.

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, HHS and FDA all have substantial responsibilities in assuring compliance with ethical and legal standards. In addition, one body--the Institutional Review Board--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 Hospital Institutional Review Board (IRB) is organized and operates under the authority of the Board of Directors of The Nebraska Methodist Hospital. The IRB's purpose and role is to review and approve (or disapprove) proposed studies to ensure that:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits;
- Selection of subjects is equitable;
- Proper informed consent will be obtained and
- Other 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, economic or educational disadvantage, or other factors.

II.
NMH IRB
STATEMENT OF ETHICAL PRINCIPLES AND POLICY

A. ETHICAL PRINCIPLES

The Nebraska Methodist Hospital ("NMH") and its Institutional Review Board 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"), a copy of which follows this Statement. 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, and the requirements set forth in the regulations of the Food and Drug Administration (21 CFR Parts 50 and 56) will be met as applicable to studies of investigational drugs and devices.

B. INSTITUTIONAL POLICY

1. 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 will be given to, without limitation, the following:

a. The risks and burdens to the subjects;

b. The anticipated benefits to the subjects and others;

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

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

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

2. NMH, 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.

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

4. NMH encourages and promotes constructive communication among the research administrators, department heads, research Investigators, clinical care staff, 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.

5. NMH, acting through the IRB, will exercise appropriate administrative overview carried out at least annually to ensure that its practices and procedures designed for the protection of the rights and welfare of human subjects are being effectively applied.

6. The IRB will 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.

7. NMH shall provide each individual at the institution conducting or reviewing human subject research (e.g., research Investigators, department heads, research administrators, research reviewers) with a copy of this statement.

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

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

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.

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

Members of the Commission

Kenneth John Ryan, M.D., Chairperson, 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.
Dorothy I. Height, President, National Council of Negro Women, Inc.
Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.
Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.
Karen Lebacqz, Ph.D., Associate Professor of Christian Ethics, Pacific School of Religion.
David W. Louisell, J.D., Professor of Law, University of California at Berkeley.
Donald W. Seldin, M.D., Professor and Chairperson, Department of Internal Medicine, University of Texas at Dallas.
Eliot Stellar, Ph.D., Provost of the University and Professor of Physiological Psychology, University of Pennsylvania.
Robert H. Turtle, LL.B., Attorney, VomBaur, Coburn, Simmons & Turtle, Washington, D.C.

Table of Contents

Ethical Principles & Guidelines for Research Involving Human Subjects

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

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

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

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

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:

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

   (b) 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.

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.

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.

---

(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.

III.
OVERVIEW

The IRB is appointed by the Board of Directors of NMH. It has authority to review, approve/disapprove and monitor on an ongoing basis, all research involving human subjects which is conducted in whole or in part by, through, or at NMH. New studies approved by the IRB are submitted to the NMH Board of Directors for approval or other action, but approval is effective once received from the IRB unless and until the approval is revoked or modified by the Board of Directors. Disapproval of a study by the IRB is generally effective without action by the Board of Directors. In addition to the IRB and the Board of Directors, and in addition to the study subject, the following individuals and entities are involved in the IRB/clinical research process:

1. **Food and Drug Administration (FDA) and HHS.** The FDA enforces federal laws governing drugs and devices. New drugs and devices can be marketed only with the FDA's approval. Prior to approval, drugs and devices go through several stages of FDA-supervised research and investigation. Under FDA regulations, there must be an Institutional Review Board which pre-approves, and supervises, the investigation conducted by local physician-investigators. The U.S. Department of Health and Human Services (HHS) imposes the same requirement for any federally-supported human research.

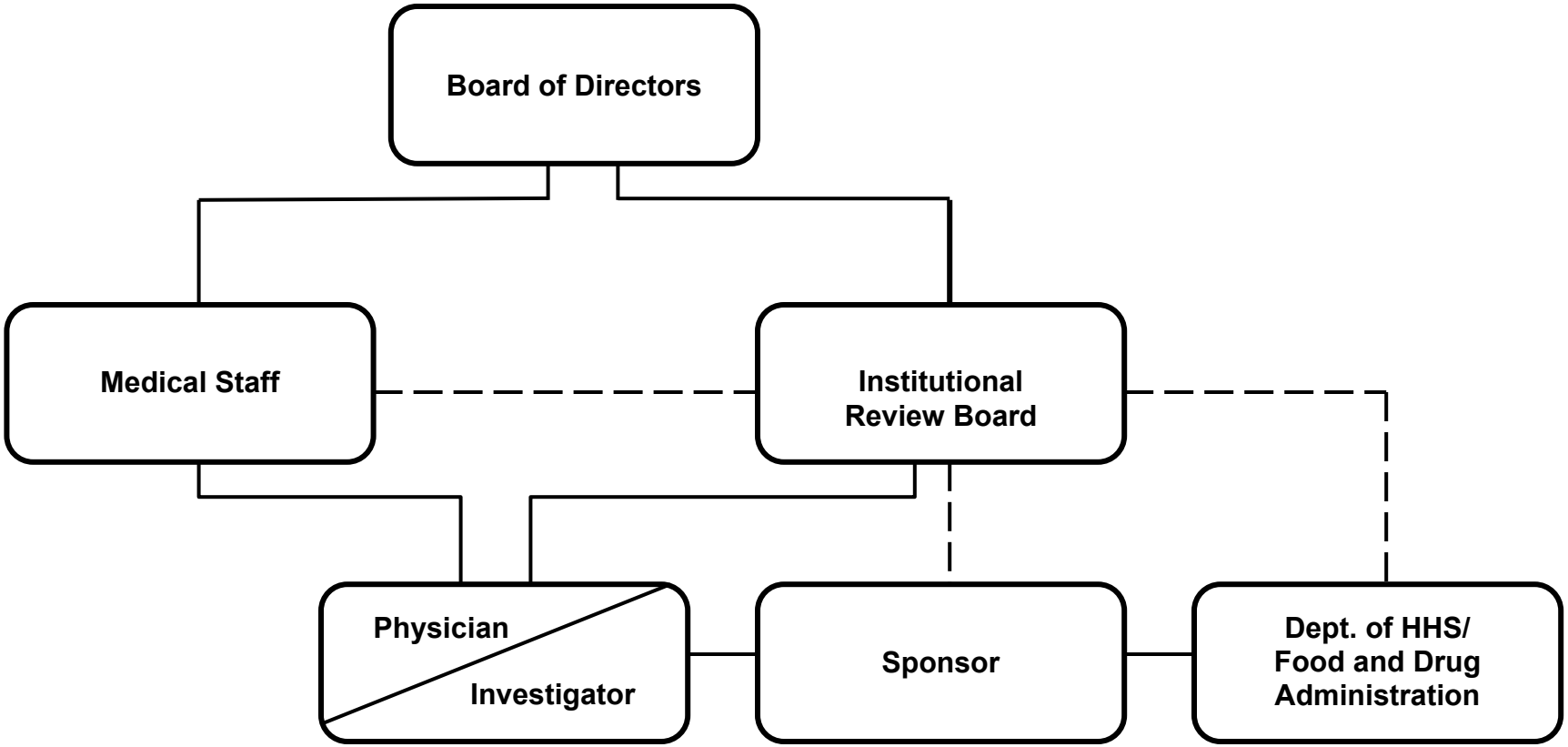
2. **Investigator.** The Investigator is the physician or other scientist responsible for the investigational use of a drug or device, or other research study, in an individual case. In sponsored studies, the Investigator has established an agreement and working relationship with the Sponsor (manufacturer or study organizer) before seeking IRB approval. Investigators are usually members of NMH's Medical Staff or otherwise separately authorized to render services at NMH, and are subject to separate NMH and/or Medical Staff credentialing. There are often several Investigators working on the same investigative protocol at NMH, a Principal Investigator and several secondary Investigators.

3. **Sponsor.** The Sponsor is the manufacturer of the investigational drug or device, or a cooperative research group or other organization which initiates and coordinates research, usually on a national or regional level. Sponsors may also be local groups or in some cases, the Investigator may also be the Sponsor. The Sponsor has primary responsibility for obtaining any required approval of the study from the FDA and/or HHS, and for reporting to the FDA and/or HHS, but the Investigator and the IRB are also subject to government supervision.

4. **Medical Staff.** The Medical Staff is entrusted by the NMH Board with primary responsibility for authorizing and reviewing physician privileges to perform patient care services in NMH. Privileges to perform procedures involving investigational drugs and devices or other studies are subject to Medical Staff review and approval the same as are other clinical privileges. Accordingly, physicians performing investigational studies operate under the concurrent authority of both the Institutional Review Board and the Medical Staff, each of which reports to the Board of Directors.

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

Nebraska Methodist Hospital
Institutional Review Board
Reporting Relationships



STRUCTURE AND OPERATIONS

A. STRUCTURE

1. **Composition.** The IRB shall have at least five (5) members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted under its review. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members including consideration of race, gender, cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. 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 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 vulnerable category of subjects, such as children, prisoners, pregnant women, or mentally disabled 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.

a. *Ex Officio* Members. *Ex officio* members shall be voting members of the IRB for so long as they hold the office or position which qualifies them for membership on the IRB, unless sooner removed by the Board of Directors. *Ex officio* members of the IRB shall consist of:

(1) NMH's Vice President of Medical Affairs/Medical Director or designee; and

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

b. 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 and at least one member whose primary concerns are in a scientific area;

(2) At least one member not otherwise affiliated with NMH, and who is not part of the immediate family of a person affiliated with NMH;

(3) At least one member who is a Registered Professional Nurse affiliated with NMH;

(4) Individuals from more than one profession and

(5) Both men and women, to the extent that this result can be accomplished through nondiscriminatory efforts.

c. Alternates. Individuals may be appointed as Alternate members of the IRB, to serve at any meeting or in any specific matter when a quorum of IRB members cannot be obtained. Alternate members shall be appointed in the same manner, and subject to the same training requirements as regular IRB members. The Chairperson may call in an Alternate member for any meeting or on any matter when a quorum is otherwise unavailable, in the Chairperson's discretion, and once called, an Alternative shall have the same duties and authority as a regular member as to that meeting or matter.

d. Expert Advice. The IRB or the Chairperson may at any time request that a study be reviewed by an outside expert (such as a specialty physician or scientist with expertise in a particular facet of the study) and consider that expert's advice and recommendations when deciding whether to approve, deny, condition or revoke approval of a study.

2. **Appointment.** Regular members of the IRB shall be recommended for appointment by the IRB and appointed by the Board of Directors. Regular members shall serve for one or more terms of three (3) years each, or until they resign or are removed from the IRB. The IRB Manager shall maintain a schedule of staggered terms so that the terms of approximately one-third of the regular members are considered for renewal or expiration each year.

3. **Training**. Ongoing training will be provided to all IRB members, including:

a. Orientation upon joining the IRB.

b. Informational discussions and news articles provided at monthly IRB meetings.

c. Periodic special meetings with guest speakers on legal/ethical/operational topics.

d. Opportunities to attend local, regional or national seminars.

e. All IRB members will be expected to successfully complete the on-line IRB training course currently offered by NMH and provide documentation of such certification to the IRB Manager. The costs of registration will be paid by NMH.

f. Every three (3) years following completion of the initial on-line IRB training, all IRB members will be expected to complete a supplemental online IRB training course and provide documentation of successful completion and re-certification to the IRB manager.

4. **Board Member Responsibilities**. Members of the IRB shall:

a. Regularly attend monthly IRB meetings and special meetings as called.

b. Review materials provided in advance of meetings as necessary to fully and meaningfully participate in the IRB's review and action on new studies, monitoring of ongoing studies, and other Board actions. Members assigned as

primary reviewers on some but not all studies will receive materials on the other studies also, and may review those materials prior to the meeting, at their discretion.

c. Participate on committees and subcommittees when appointed by the Chairperson.

d. Complete training as identified in paragraph 3 of this section.

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

f. Disqualify (recuse) themselves from action on studies where the member has a conflict of interest as described in paragraph 5 of this section.

g. Advise the Chairperson 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 Chairperson any prospective candidates for appointment to the IRB.

h. 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 Handbook.

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

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

b. Such member is directly associated through family relationship, professional association (partnership or professional corporation) or financial interest with the sponsor or Investigator; or

c. 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.

The fact that one or more members of the IRB may be disqualified from participating in the IRB's review or monitoring of a given study, shall not impair the ability of the IRB to proceed with the study, provided there is a quorum consisting of members who are not disqualified. Any member having such a conflict of interest may provide information requested by the IRB, and will generally be expected to do so as would any other Investigator; and as with any other Investigator, may in the discretion of the remaining IRB members, be asked to remain present or excuse himself or herself from the meeting during the IRB's deliberations and vote on the study.

6. **Vacancies.** Vacancies on the IRB may be filled by the Board of Directors of NMH upon recommendation of the IRB. A member recommended by the IRB to fill a vacancy occurring during an interval prior to Board approval may serve as a temporary member with full voting privileges pending approval by the Board of Directors.

7. **Chairperson.** The Board of Directors shall appoint a member of the IRB to serve as Chairperson of the IRB, who shall have and exercise all duties which are traditionally held by a committee Chairperson or are specifically granted by these guidelines or applicable regulations; and in the event of the Chairperson's absence or disqualification, NMH's Vice President of Medical Affairs/Medical Director shall assume and discharge the Chairperson's duties.

B. OPERATIONS

1. **Meetings.** The IRB shall schedule and hold regular meetings at times to be determined by the Chairperson, usually on a monthly basis, and may schedule and hold special meetings at such other times as may be necessary to discharge its duties. Special meetings may be called by the Chairperson at any time upon the Chairperson's initiative, or at the request of any IRB member or any NMH official involved in a study under the IRB's authority.

2. **Quorum and Vote.** In order to conduct business, the IRB shall meet both a numerical quorum and a compositional quorum.

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.

All actions of the IRB require the affirmative vote of two-thirds (2/3) of those members present and voting at a time when a quorum is present.

3. **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.

4. **Authority of Chairperson Between Meetings.** The Chairperson of the IRB, or the Vice President/Medical Director of NMH in the absence of the Chairperson, 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 Chairperson. The Chairperson may:

a. Emergency Use. Concur with the use of an investigational drug or device which has not been previously approved by the IRB, on an emergency basis, where the criteria for Emergency Use outlined in Part IV of this Handbook have been met.

b. Expedited Review. Review and approve any of the following on an expedited basis:

(1) Studies which are eligible for Expedited Review under the criteria outlined in Part IV of this Handbook.

(2) Modifications to previously approved studies, if in the opinion of the Chairperson, the modification does not appear to substantially increase patient risk or discomfort. This includes, but is not limited to, editorial and administrative changes and non-material changes to the Investigation Brochure, as well as changes to informed consent documents where the changes do not materially alter the risk-benefit analysis or are conforming to standard consent language previously approved by the IRB.

(3) Study closures where there have been no subjects enrolled locally.

(4) Adverse event reports. The Chairperson may appoint a committee to assist with reviews of adverse event reports. The IRB shall be briefed at its next regular meeting regarding adverse event reports reviewed, conclusions and recommendations by the reviewers, and any action taken or recommended which requires IRB approval.

The Chairperson shall report to the IRB on all matters approved on an expedited basis. The Chairperson may remove any matter from expedited status and require that it undergo full IRB review at any time. Matters reviewed on an expedited basis may only be DISAPPROVED by action of the full IRB at a regular or special meeting.

c. Secondary Site Studies. Approve secondary site studies. (See Part IV.)*

d. Other Authority. Take any other action and exercise any other authority delegated to him or her by the IRB, or in these Guidelines.

The Chairperson may consult with any other IRB member, NMH staff member or other person before taking such action, in his or her discretion.

5. **Guidelines and Procedures.** The IRB may at any time adopt additional guidelines, policies, procedures and criteria for the conduct of its business and for the submission, review and monitoring of studies.

IV.
HOW STUDIES ARE CLASSIFIED, SUBMITTED, REVIEWED AND MONITORED

A. IDENTIFYING STUDIES WHICH CONSTITUTE RESEARCH AND REQUIRE IRB APPROVAL

1. **Scope of the IRB's Authority**. All human subject research studies which are conducted in whole or in part at NMH, or under the direction of any employee or agent of NMH in connection with his or her institutional responsibilities or using any property or facility of NMH, must first be submitted to the IRB for review and approval. This includes, but is not limited to, studies for which IRB review is required under regulations of the FDA or HHS.

The IRB may also, in its discretion, accept authority over studies for which IRB review is required under the regulations and in which members of the NMH Medical Staff 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, NMH.

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

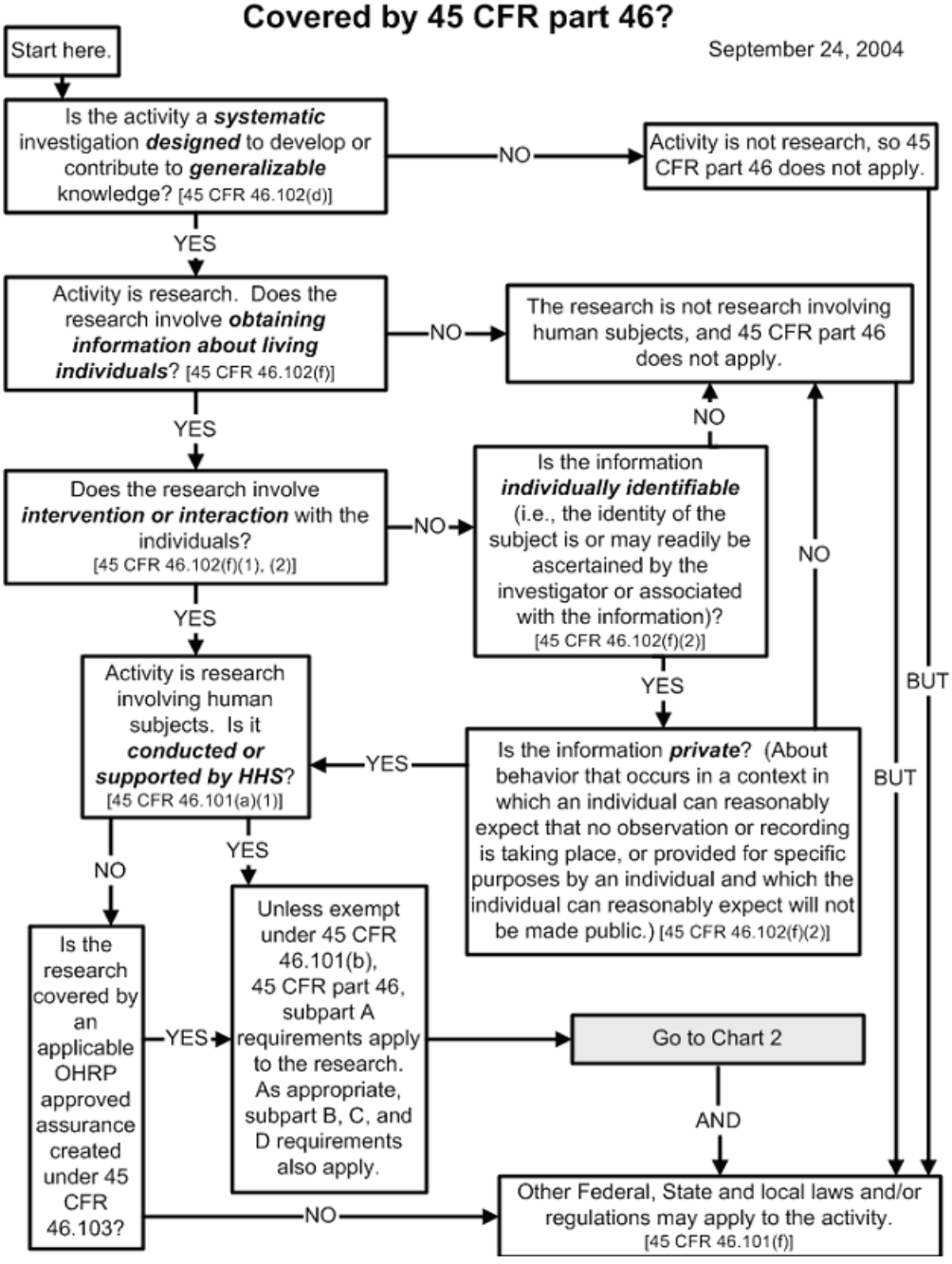
2. **Associate Institutions**. The IRB may, in its discretion, approve another institution as an affiliate or performance site for one or more studies under the authority of the IRB. Such approval shall authorize the accrual of subjects at the other institution into designated studies, and the appointment of physicians at the other institution as secondary Investigators. Such approval shall be subject to the approval of NMH administration, and shall be conditional upon the other institution and the Investigators agreeing to comply fully with all guidelines, standards, policies and procedures established by the IRB; agreeing to cooperate fully with the IRB, the Principal Investigator and NMH in conducting the investigation, reporting data and providing access to records; and executing any other agreements requested by the IRB or NMH in connection with the study.

3. **Definition of Research**. "Human subject research" includes any systematic investigation involving interaction or intervention with human subjects, or utilizing identifiable private information of human subjects, which is designed, in whole or in part, 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.

The U.S. Department of Health and Human Services, Office of Human Research Protection (“OHRP”), has published a Decision Chart to help determine whether a particular activity constitutes research involving human subjects. That chart is presented on the following page.

Some research is exempt from IRB review requirements, and some is eligible for expedited review. These categories are discussed in more detail at Part B, below.

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



B. STUDIES WHICH ARE ELIGIBLE FOR ABBREVIATED REVIEW

1. **Exempt Research**. Only a few very limited categories of human subject research are completely exempt from IRB review under federal regulations. The NMH IRB follows the federal guidelines and exempts only the following research from IRB review (for more detailed descriptions refer to the regulations at 45 CFR 46:101(b)):

a. Research involving the use of educational tests, if subject identity and privacy are protected and other specified conditions are met.

b. Research utilizing only existing data and records if subjects cannot be identified directly or indirectly or the data/documents are publicly available.

c. Other categories identified in the regulations which are not likely to occur at NMH (e.g., research on public benefit programs, research occurring in an educational institution or consumer food preference studies).

See OHRP Decision Charts 2-7, on the following pages, for determination of whether research is Exempt.

All proposed research which may be exempt from IRB review must be presented to the Chairperson of the IRB before the research is initiated, for confirmation that the research is exempt, and for the Chairperson's approval to proceed with the research at NMH.

Chart 2: Is the Research Involving Human Subjects Eligible for Exemption Under 45 CFR 46.101(b)?

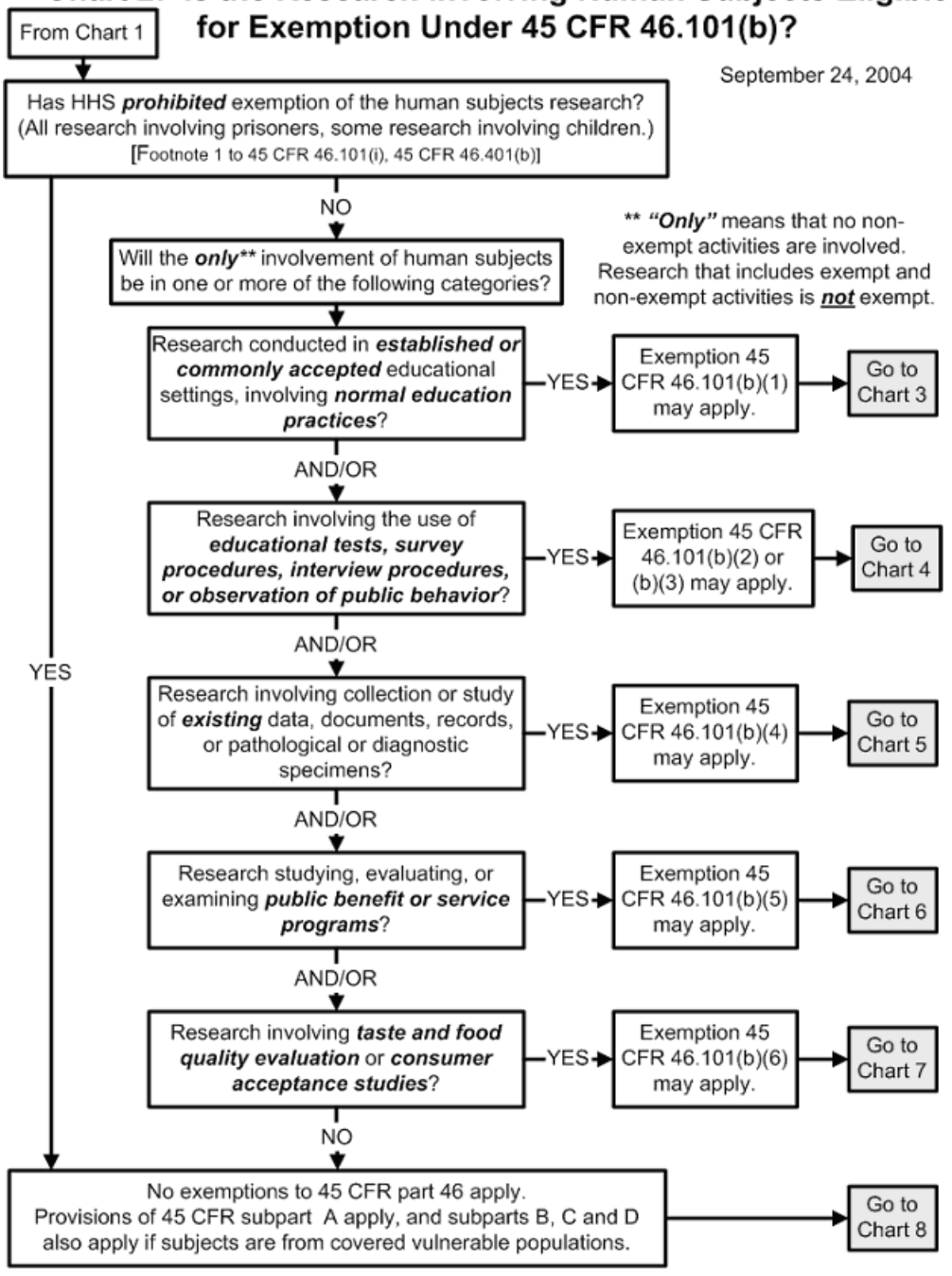
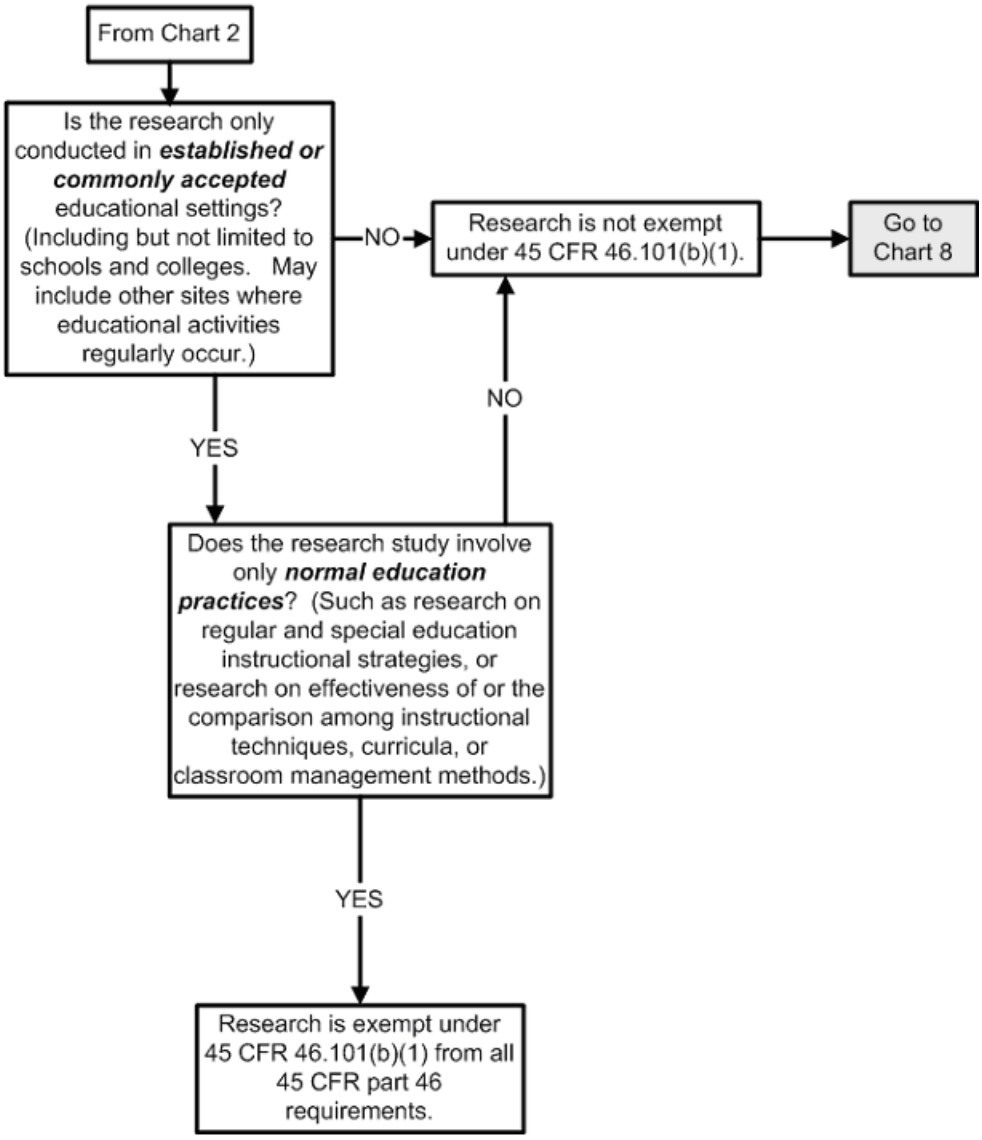
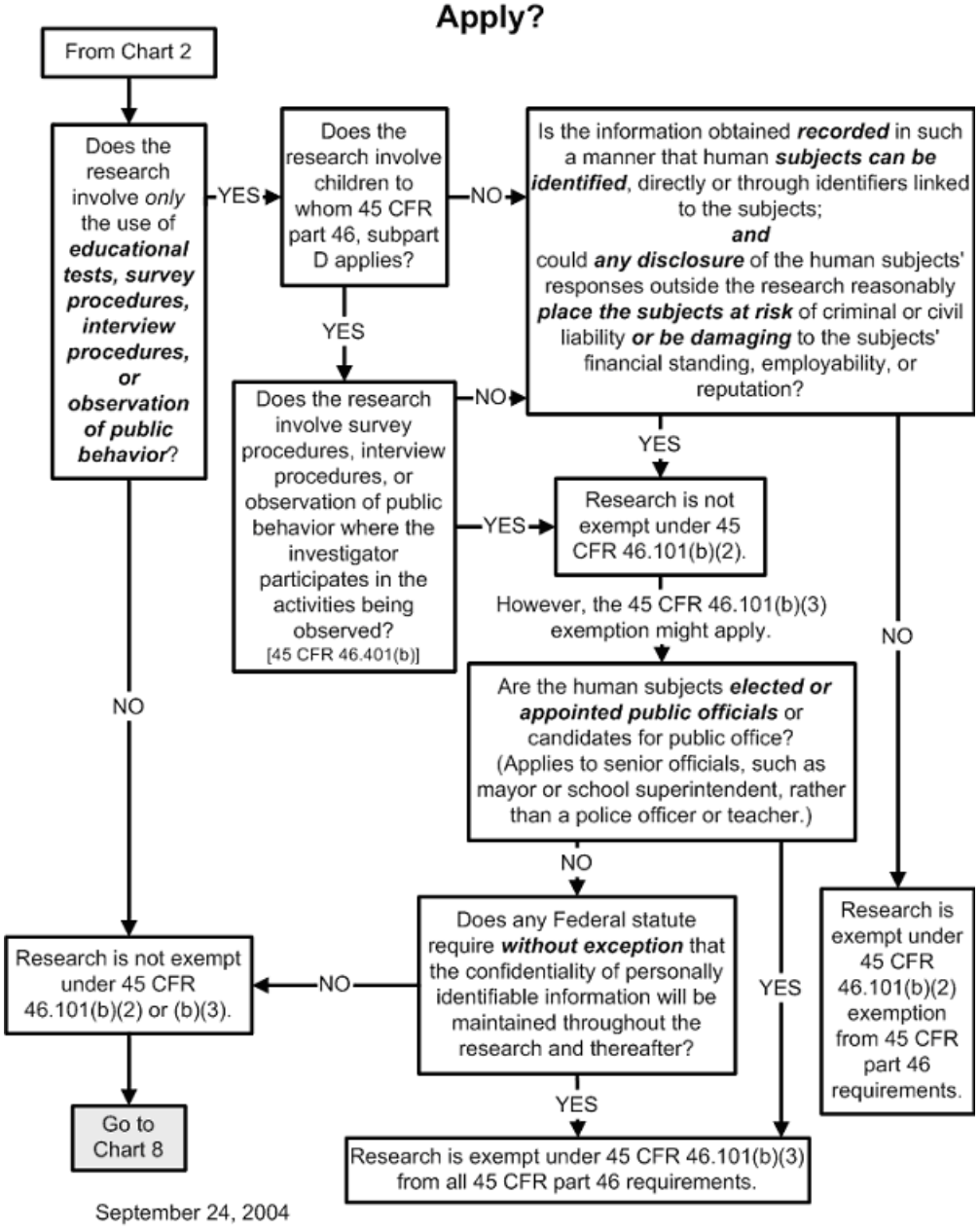


Chart 3: Does Exemption 45 CFR 46.101(b)(1) (for Educational Settings) Apply?



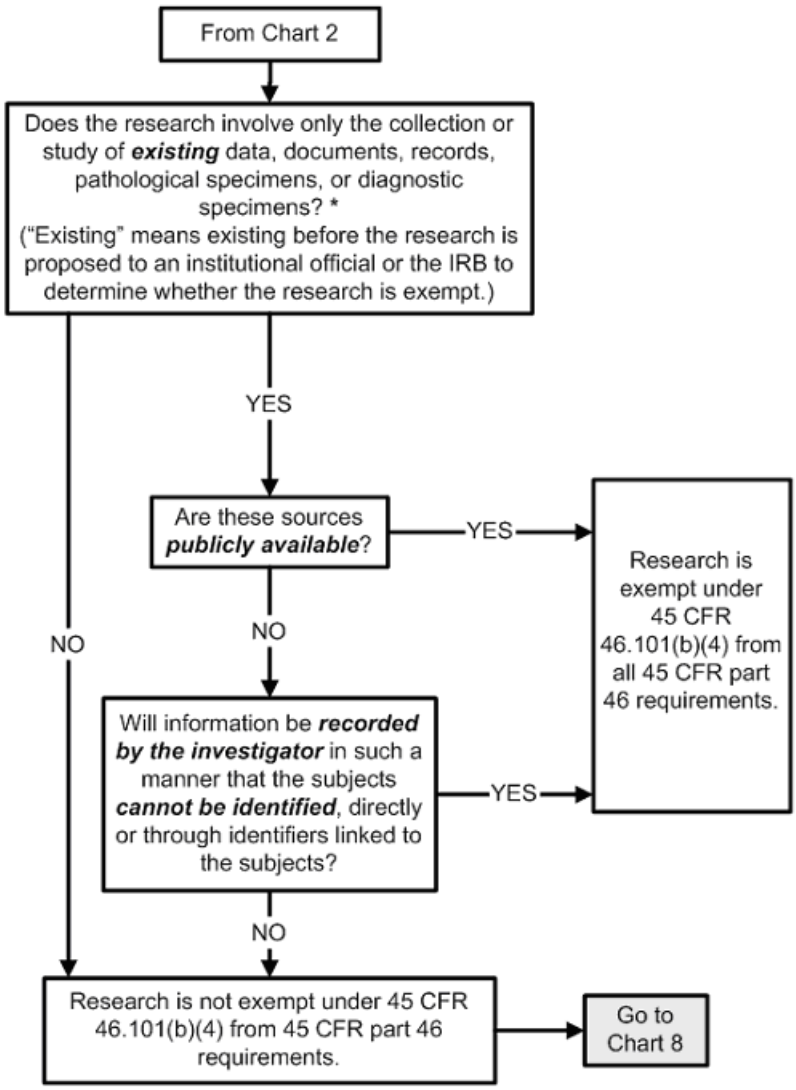
September 24, 2004

Chart 4: Does Exemption 45 CFR 46.101(b)(2) or (b)(3) (for Tests, Surveys, Interviews, Public Behavior Observation) Apply?



September 24, 2004

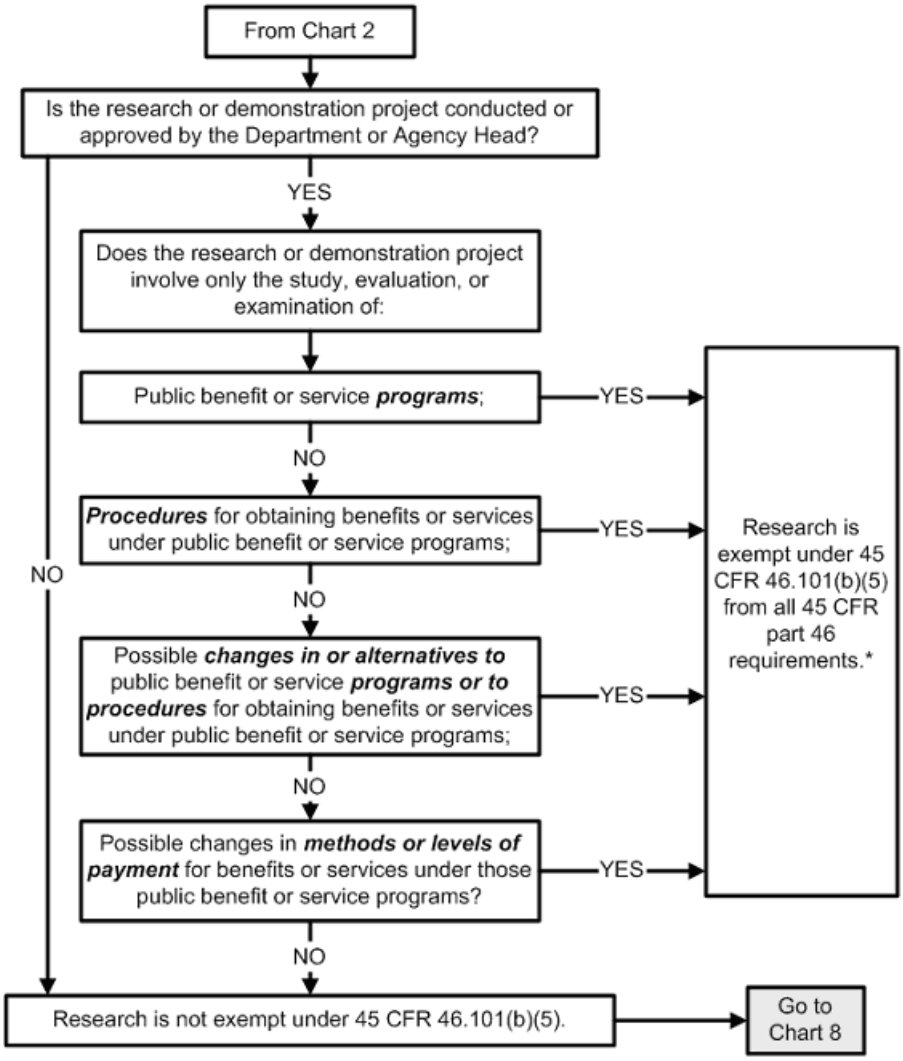
Chart 5: Does Exemption 45 CFR 46.101(b)(4) (for Existing Data Documents and Specimens) Apply?



* Note: See **OHRP** guidance on research use of stored data or tissues and on stem cells at http://www.hhs.gov/ohrp/policy/index.html#tissues and #stem, and on coded data or specimens at #coded for further information on those topics.

September 24, 2004

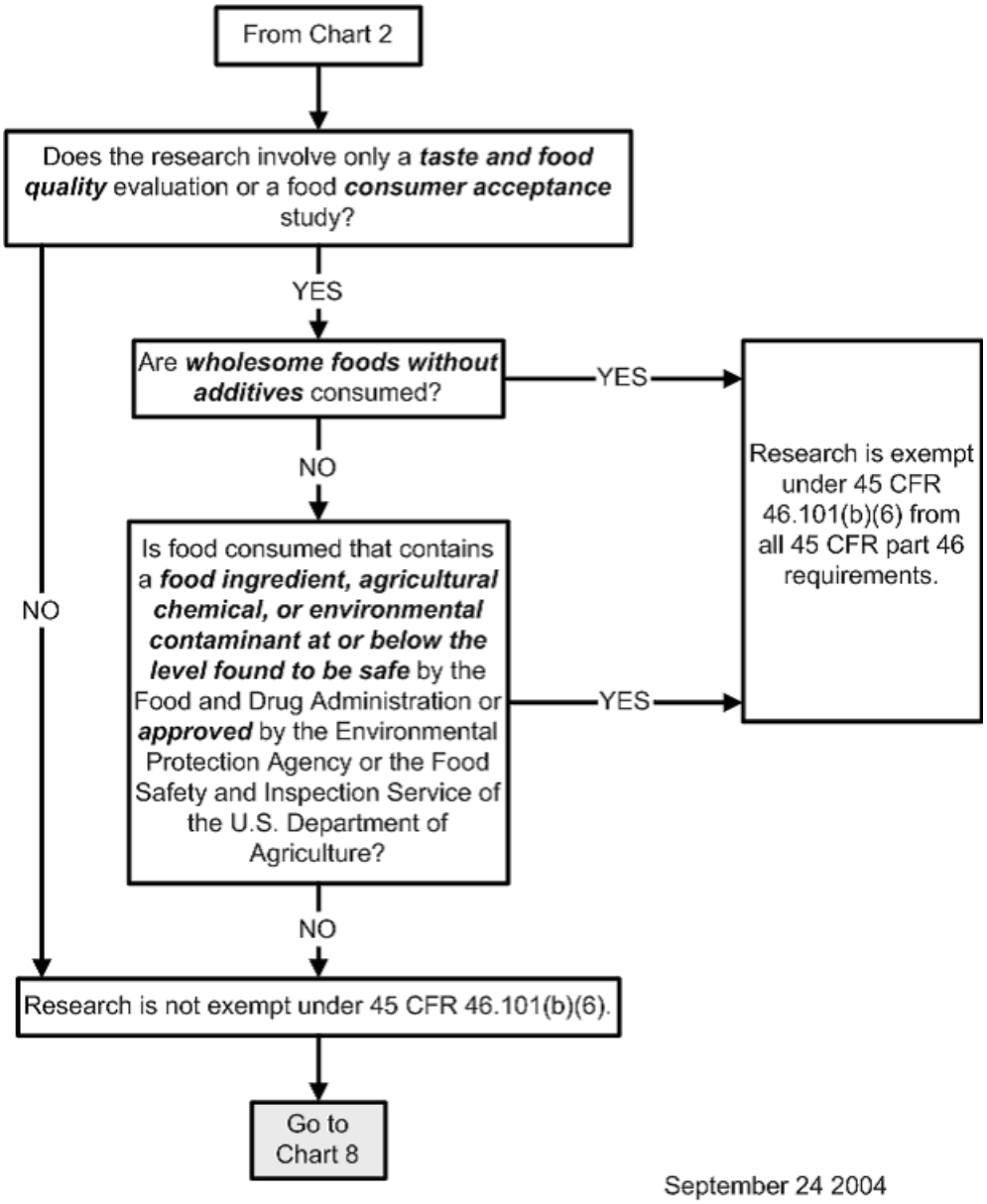
Chart 6: Does Exemption 45 CFR 46.101(b)(5) (for Public Benefit or Service Programs) Apply?



* Note: See **OHRP** guidance on exemptions at http://www.hhs.gov/ohrp/policy/index.html#exempt for further description of requirements for this exemption.

September 24, 2004

Chart 7: Does Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies) Apply?



September 24 2004

2. **Expedited Review**. Certain research activities involving minimal risk to subjects or minor changes in previously approved research may be reviewed and approved by the Chairperson without full IRB approval. The Chairperson reports such action to the full IRB, which may ratify, reverse or modify the Chairperson's actions. The Chairperson 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. Studies approved on an expedited basis are subject to the same reporting requirements (annual reviews, modifications, adverse events) as other studies.

a. Minimal Risk Defined. "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. Research activities that are "low risk" relative to other research activities are sometimes mistakenly considered minimal risk; in an effort to provide clear standards and to minimize confusion, full IRB approval will be required for any research that involves any of the following:

(1) Administration of any investigational new drug except as provided in b(5)(b), or administration of any non-investigational drug for research purposes.

(2) Use of any investigational device except as provided in b(5)(c), or use of any non-investigational device on a human subject for research purposes.

(3) Obtaining any blood, body fluid or tissue from a human subject unless collected only in a manner specifically listed in section b(iv) below (use of blood or tissue which has already been obtained as a byproduct of a non-research procedure may be eligible for expedited review, as in a secondary site study).

(4) Obtaining information or data from direct interaction with human subjects such as through interviews, questionnaires, telephone calls (use of existing data from existing records may be eligible for expedited review).

b. Categories of Research Eligible for Expedited Review. The following categories of research are eligible for expedited review (note that reporting on Exempt Research and Emergency Use is also handled by the Chairperson without full IRB review, but is not labeled "Expedited Review"):

(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) Continuing review of previously approved research (annual reports) where the study is permanently closed to enrollment, all subjects have completed research-related interventions, and the study remains open

only for long-term follow-up; or no subjects are enrolled locally and no additional risks have been identified; or the remaining research activities are limited to data analysis.

(3) Follow-up reporting on approved HDE (Humanitarian Device Exemption) activities.

(4) Secondary Site studies.

(5) Other new studies in the following categories as defined by federal regulations:

(a) The following activities 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. 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.

(b) Clinical studies of drugs for which an investigational new drug application is not required.

(c) Clinical studies of medical devices for which (i) an investigational device exemption application is not required; or (ii) the medical device is cleared or approved for marketing and the medical device is being used in accordance with its cleared or approved labeling.

(d) Collection of blood samples by finger stick, heel stick, ear stick or venipuncture from healthy, non-pregnant adults who weigh at least 110 pounds (for these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week); or from other adults and children if the risk is minimal 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).

(e) Prospective collection of biological specimens for research purposes by non-invasive means. Examples include:

(i) hair and nail clippings in a nondisfiguring manner

(ii) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction

(iii) permanent teeth if routine patient care indicates a need for extraction

(iv) excreta and external secretions (including sweat)

(v) 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

(vi) placenta removed at delivery

(vii) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor

(viii) 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

(ix) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings

(x) sputum collected after saline mist nebulization

(f) 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 or approved by 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 include:

(i) 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

(ii) weighing or testing sensory acuity

(iii) magnetic resonance imaging

(iv) electrocardiograph, electroencephalography, thermography, detection of naturally occurring radioactivity,

electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography

(v) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

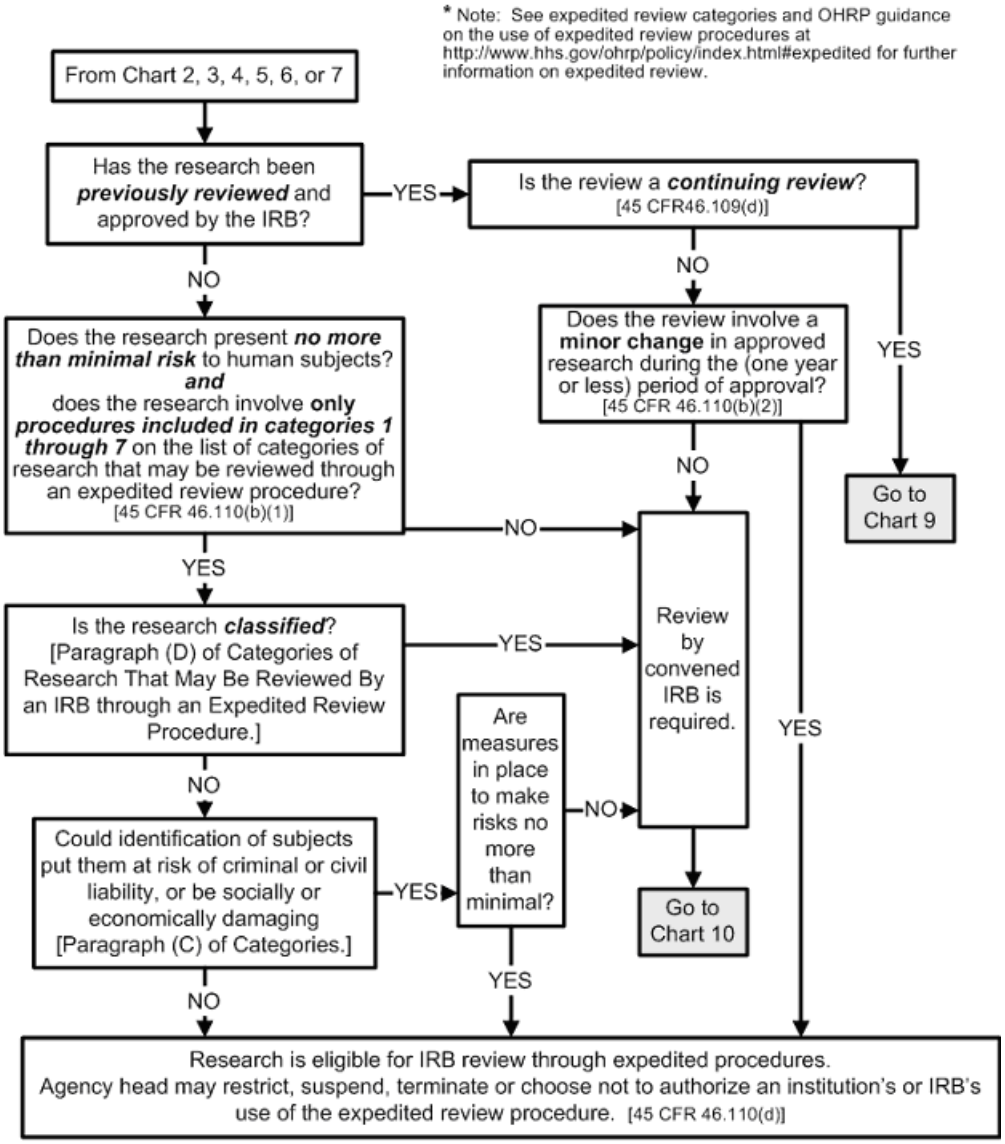
(g) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

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

(i) 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.

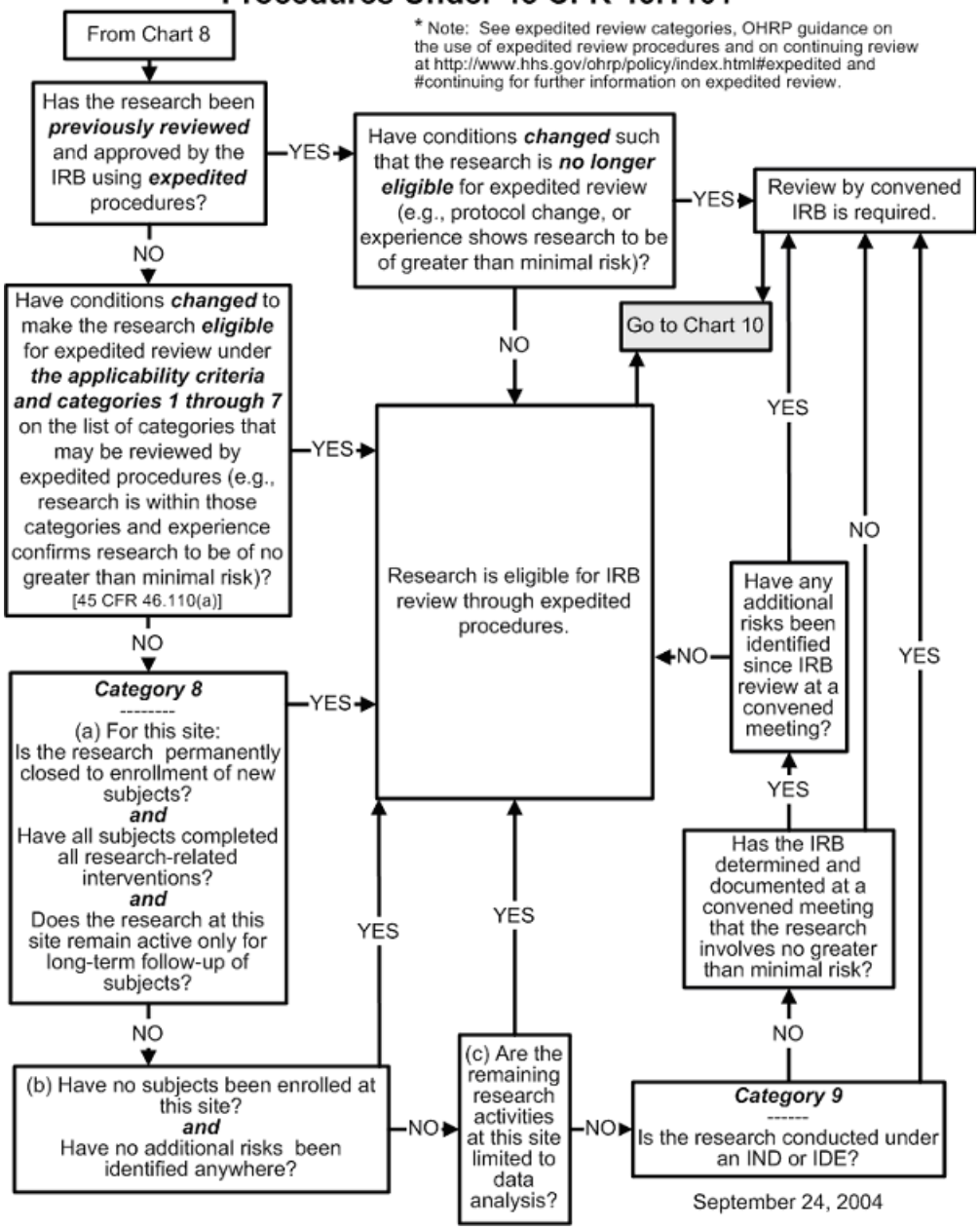
See OHRP Decision Charts 8 and 9, on the following pages, for analysis of when expedited procedures can be followed.

Chart 8: May the IRB Review Be Done by Expedited Procedures Under 45 CFR 46.110?*



September 24, 2004

Chart 9: Can Continuing Review be Done by Expedited Procedures Under 45 CFR 46.110?



3. **Compassionate Use.**

a. Compassionate Use. The term "compassionate use" is often used within the medical and research communities, to describe the use of an investigational drug for a single patient or a few patients who are very ill and have no other viable treatment options. Occasionally, physicians will contact the IRB or its Chairperson for approval of a compassionate use. Surprisingly, however, the term "compassionate use" is not formally recognized in the applicable statutes or regulations, and therefore has no legal meaning on its own; **neither the IRB nor its Chairperson have approval authority on this basis alone. Accordingly, when a physician is faced with a compassionate use situation, it is important to identify the specific legal context of that use, in order to determine the role, if any, of the IRB.**

b. Types of Uses Considered "Compassionate." The following situations are those which are typically identified as compassionate uses. The legal recognition given to each, and the implications for IRB review and approval, are as follows:

(1) Emergency Use. The FDA regulations allow for a test article to be used in emergency situations without prior IRB approval, provided that the emergency use is reported to the IRB within five (5) working days; subsequent use of the test article must be reviewed by the IRB. An emergency is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. **Physicians using an investigational drug on an emergency basis must notify the IRB Chairperson within five (5) working days.** The IRB Chairperson will so notify the IRB at its next meeting. As a general rule, full IRB approval should be sought if this type of use is likely to occur a second time (See Section 4, below, for more details.)

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

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

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

c. Limited Authority of IRB Chairperson. The Chairperson of the IRB does not have the authority to unilaterally grant approval to any compassionate use without full IRB review and approval. However, the IRB Chairperson may:

(1) Receive reports of emergency uses, as described in the preceding section on emergency use, and then to report that use to the IRB at its next meeting.

(2) Assist the Investigator/physician in determining which category applies to the proposed compassionate use, and therefore which procedures to follow.

(3) Assist in bringing before the full IRB, those matters which require IRB approval.

Summary of Typical Compassionate Use Situations

Use Type	IRB Role	Authority of IRB Chairperson
Emergency Use	Investigator must report to IRB within 5 days of use; if similar emergency use is likely to arise, full prospective IRB review and approval should be obtained.	Receives report of use from Investigator; relays information to IRB at its next regular meeting. No individual approval authority.
Single Patient Use	No IRB approval required. All approvals come from the FDA and the Sponsor.	No individual approval authority. Available for consultation on procedural issues.
Treatment IND	Full prospective IRB review and approval is required like any other research study.	No individual approval authority. Available for consultation on procedural issues.

4. **Emergency Use.** Following are additional details published by the FDA, regarding the procedures which apply to an emergency use of an investigational drug:

a. Emergency use is defined as the use of a test article (e.g., investigational drug or biologic) on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval for the use. The Investigator is still required to obtain informed consent under these circumstances.

b. The FDA exempts from IRB review the emergency use of a test article so long as the emergency use is reported to the IRB within five working days of its occurrence. Any subsequent use of the test article is subject to IRB review [21 CFR 50.23; 21 CFR 56.104(c)]. "Subsequent use" means any use of the test article that occurs after its initial emergency use.

c. Should a situation arise which would require the emergency use of the test article for a second patient, either by the same or a second physician, or the same test article, subsequent emergency use should not be withheld for the purpose of gaining IRB approval. If it appears probable that similar emergencies will require subsequent use of the test article at the institution, every effort should be made either to sign on to the sponsor's protocol or to develop a protocol for future emergency use of the article at the institution. Either of these protocols would need to be prospectively reviewed and approved by the IRB for future use of the test article.

d. In emergency circumstances, it may not be feasible to obtain informed consent prior to using the test article. The regulations therefore provide an exemption from the informed consent requirement for such situations. Emergencies qualifying for this exemption are defined as: (1) life-threatening situations necessitating use of the test article; (2) where the subject is unable to provide effective consent; (3) there is insufficient time in which to obtain consent from the subject's legal representative; and (4) there is no available alternative method of approved or generally recognized therapy of equal or greater likelihood of saving the subject's life [21 CFR 50.23(a)(1)-(4)].

e. Special procedures for documenting the unfeasibility of obtaining consent apply as follows: The Investigator and a physician who is not participating in the clinical investigation must certify in writing the existence of all four conditions listed above before use of the test article [21 CFR 50.23(a)]. If in the Investigator's opinion immediate use of the test article is necessary to save the life of the subject and there is insufficient time to obtain the independent determination required by § 50.23(a) before using the test article, the Investigator is to make his or her own written determinations, then obtain the written review and independent evaluation of a physician who is not participating in the clinical investigation within five working days after the use of the test article [21 CFR 50.23(b)]. The documentation required by either § 50.23(a) or § 50.23(b) must be submitted to the IRB within five working days after the use of the test article [21 CFR 50.23(c)].

The use of a test article in an investigation designed to be conducted under emergency conditions (e.g., emergency room research) usually does not qualify for the emergency use exemption.

5. **Humanitarian Use Device**. In some cases the FDA will grant a "Humanitarian Device Exemption" ("HDE") to a new medical device, to simplify the premarket approval process for devices with limited numbers (4,000 or less per year) eligible patients. These are known as "Humanitarian Use Devices" ("HUD"). Use of an HUD under an HDE initially requires full IRB review and approval (not expedited review)

but the usual informed consent document requirements do not apply if the device is not being used in a research study unless the IRB determines otherwise (the physician is still well-advised to fully inform the patient of the unique status of the device). Continuing review following initial IRB approval may be expedited by the Chairperson.

6. **Secondary Site Studies**. "Secondary Site Studies" refer to studies which have already been subjected to full review and approval by another qualified IRB, and in which:

a. Tissue or Data Collection Only. Limited study activity will occur at NMH, such as tissue collection or record-keeping; or

b. Accrual Only. Physicians at NMH will be asked to accrue and consent patients at NMH to participate in the study entirely at the other institution's site.

The Chairperson may accept approval by another IRB and waive the requirement of approval by the NMH IRB for involvement solely as a secondary site, under the following conditions and subject to the following limitations:

c. The Investigator(s) must submit to the Chairperson of the IRB a written summary of the study satisfactory to the Chairperson; the protocol under which the study is being conducted at the supervising institution; 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; and the proposed informed consent document. The informed consent document must clearly authorize the activity which will occur at NMH (e.g., transmittal to the other institution of tissue removed during surgery at NMH) and must comply with usual IRB standards for informed consent and HIPAA authorization.

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

e. The Investigator(s) must have necessary privileges through normal Medical Staff channels commensurate with their planned activities at NMH.

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

Upon receipt of all required information, the Chairperson may accept the other IRB's review of the secondary site study, subject to any limitations he or she deems appropriate, or the Chairperson may require full review and approval by the full IRB before any part of, or support for, the study proceeds at NMH. The Chairperson's action shall be effective when taken, subject to the authority of the full IRB to later rescind or modify such action

The Chairperson shall report such action to the full IRB. The IRB may approve the Chairperson's actions in whole or in part, may require changes, may require that additional information be provided to the IRB, and/or may require that the study be submitted to the IRB for full review before it is continued at NMH. Acceptance of secondary site studies based on another IRB's approval may be suspended or withdrawn at any time, by the Chairperson or by the IRB.

C. SUMMARY OF THE REVIEW PROCESS

The following chart summarizes the review and approval procedures for various categories of research. Please review the detailed explanations of each category in this Handbook Part IV. Except for "emergency use" and "single patient use," fully completed IRB forms and complete supporting documents are required in all cases.

Category		IRB Review/Approval Process
Exempt Research		Abbreviated approval by the IRB Chairperson. Contact the Chairperson to discuss the required information and documentation. No ongoing review required.
Expedited Approval		Review and approval by the IRB Chairperson, which occurs more quickly than full IRB approval. Limited to narrow categories of research. Full IRB review forms and supporting documents required. Annual reporting and ongoing review.
"Compassionate" Uses (See Section D.3)	Emergency Use	IRB approval not required. Must be reported to IRB Chairperson within 5 days. No ongoing review or reporting. Generally, one-time only.
	Single Patient Use	IRB approval not required. All approvals come from FDA and Sponsor. IRB Chairperson available for consultation (optional).
	Treatment IND	Full IRB review required. Complete IRB forms and documents. Annual reporting and ongoing review. Chairperson cannot approve on an expedited basis.
Humanitarian Devices		In some cases the FDA will grant a "Humanitarian Device Exemption" ("HDE") to a new medical device, to simplify the premarket approval process for devices with limited numbers (4,000 or less per year) of eligible patients. These are known as "Humanitarian Use Devices" ("HUD"). Use of an HUD under an HDE initially requires full IRB review and approval (not expedited review) but the usual informed consent document requirements do not apply if the device is not being used in a research study unless the IRB determines otherwise (the physician is still well-advised to fully inform the patient of the unique status of the device). Continuing review following initial IRB approval may be expedited by the Chairperson.
Secondary Site Studies		Expedited approval available from IRB Chairperson. Documentation and process will depend on the nature of the activity at NMH.
All Other Research		Full IRB review. Complete forms and documents required. Annual reporting and ongoing review.

Summary-- Expedited vs. Full Review	
Chairperson Only	Full IRB
• Exempt Research (Initial Review Only) • Expedited Matters (See Section D.2 for list. Ongoing reporting duty) • Emergency Use (Notification only) • Secondary Site Studies (See Section D.5)	• Treatment IND. • Humanitarian Device Exemption (HDE) initial approval only • Waivers of Consent (See Part V Section G) • All Other Research
No Required Review: Single Patient Use	

D. SUBMISSION AND REVIEW OF STUDIES

Before undertaking a human research study, an Investigator shall submit a complete application for IRB approval, which shall include an investigational plan or research plan, a report of prior investigations or research, a proposed informed consent document together with such additional information as the IRB may require, the Investigator may deem appropriate, or as required by applicable FDA or HHS regulations.

1. **Procedure for Submission**.

a. Request for Review form (Part VII, Form 1) is submitted to the Medical Staff office no later than the second Monday of the month, for review by the IRB at its regular monthly meeting. The Request for Review form must be FULLY completed and signed, and accompanied by:

(1) The complete study protocol and any amendments to date, together with reports of prior investigations and sponsor approval reports/letters.

(2) The proposed informed consent document.

(3) For any listed Investigators who are not currently Medical Staff members in good standing at NMH, their complete and current curriculum vitae.

(4) Any other information requested by or on behalf of the IRB.

(5) Any other information the Investigator deems helpful.

(6) The Fee for Industry-Sponsored Studies will be forwarded following IRB approval and signing of a contract with the study Sponsor.

b. The Principal Investigator will be expected to attend the IRB meeting at which the proposed study will be considered, to provide an overview and explanation of the study and to answer questions.

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

a. Whether the information submitted to the IRB concerning the study contains any untrue statement of a material fact or omits material information required by the IRB or the regulations;

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

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

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

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

f. 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:

(1) The risks to the subjects are minimized by using procedures which are consistent with sound research design and do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;

(2) The risks to the subjects are reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge to be gained;

(3) Selection of subjects is equitable, with particular attention to the special problems of research involving vulnerable populations such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons;

(4) The rights and welfare of subjects will be adequately protected, with particular safeguards included for the protection of any vulnerable populations;

(5) Legally effective informed consent will be obtained and documented by adequate and appropriate methods in accordance with the provisions of federal regulations;

(6) The conduct of the activity will be reviewed at timely intervals;

(7) Participation in the study does not result in an inappropriate financial burden to the subject;

g. Whether provision has been made in the study or by the IRB or others for prompt reporting to the IRB, the Investigator, appropriate NMH officials, the FDA, 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

h. 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 (see Investigator Responsibilities and Standards, paragraph E), and conflicts which may be created by the payment of fees or other benefits to the study subject.

3. **Approval and Disapproval.** Based upon the investigational or research plan, the report of prior investigations or research and such other information as it considers relevant, the IRB shall APPROVE, CONDITIONALLY APPROVE or DISAPPROVE the study. The IRB may request additional information if it does not believe that it has adequate information on which to base a decision, and may TABLE any study pending receipt of information.

a. Approval. Approval shall entitle the Investigators to participate in the study subject to any conditions or modifications imposed by the IRB, and with the approval of the sponsor. Unless otherwise specified by the IRB, approval by the IRB is effective immediately, subject only to the authority of the Board of Directors of NMH to revoke approval or impose additional conditions or modifications. Approval to accrue patients at an affiliate institution shall be subject to any additional conditions or authorizations required by that institution, including review by its own institutional review board, if applicable.

b. Disapproval. Prior to receipt of approval, or in the case of disapproval, the Investigator shall not proceed with the study at NMH, or utilizing any resources of NMH, or at any affiliate institution unless separately approved by that institution as an independent study. The Investigator may request reconsideration and may submit additional information to the IRB, but the final decision of the IRB shall be binding upon the Investigator.

4. **Report.** Where the IRB has approved or conditionally approved a proposed study, the IRB shall forward to the Investigator a written report of its actions and any conditions imposed. A copy of the Handbook for IRB Members and Investigators shall be provided to all Investigators of approved studies. The IRB may correspond or deal directly with Medical Staff or other NMH officials, the sponsor, the FDA, and/or HHS in answering questions or resolving conflicts regarding the scope of approval, and in making other reports which may be required or appropriate from time to time.

5. **Fees for Industry - Sponsored Studies**. In order to defray administrative costs, and consistent with generally accepted IRB practices, the NMH IRB requires a one-time fee for the submission of new protocols in the sum of $2000.00. This fee applies to industry-sponsored studies, i.e., studies sponsored by a pharmaceutical company, device manufacturer or other private industry. This fee does not apply to studies sponsored by a nonprofit cooperative research group or local physician-Investigators. The Chairperson of the IRB shall resolve any question as to whether the fee applies to a particular study. The fee is due upon submission of the Request for Review, except in the case of industry-sponsored studies which shall pay the fee following IRB review and signing of a contract. Two-thirds of the fee ($1320.00) may be refunded if the study is disapproved; if requested by the Sponsor, no part of the fee is refunded once the study is approved, even if it is later suspended or approval is revoked.

E. PHASE I STUDIES. Research studies are categorized by phase. Phase I studies are usually the first trials of a drug or treatment on humans and are used to establish whether a treatment is safe and at what dosages. Phase II studies assess the efficacy of treatments after their safety and feasibility has been established in Phase I studies, Phase II Studies compare effective treatments from Phase II studies to currently accepted “standard of care” treatments. Phase IV studies collect and compare data on established treatments.

Most Phase I studies treat cohorts of subjects in small groups of three to six at predefined dose levels. The studies typically start at very low doses that were minimally toxic in animal studies. If that dose is found to be safe, additional cohorts of subjects will be treated at higher doses with escalation continuing until a maximum tolerated dose is defined or the study is discontinued due to unacceptable toxicities.

Due to the significant risks for subjects in Phase I trials, separate procedures have been developed for Phase I studies and/or for Phase I of a combined Phase I/Phase II trial. Patients who enter Phase I studies need to be fully informed that these studies usually represent the initial clinical experiments in humans. The possibility that unknown and unpredictable side effects may occur must be stated. Subjects should also be advised that there is a very minimal (if any) chance that participation in the study will be of medical benefit to them personally. The overriding benefit of the study is to contribute to the knowledge base about new treatments that may be of benefit to patients in the future.

In order to avoid unnecessary risks to subjects during dose escalation Phase I studies, the number of secondary investigators will be limited to approximately five.

The maximum period of approval will be six months, with mandatory review by the IRB at that point.

F. CONTINUING REVIEW AND MONITORING

The IRB shall review each approved study according to a schedule adopted by it, but not less frequently than annually. The requirement of ongoing review shall continue until the study is completed or discontinued.

1. **Procedures for Ongoing Reporting**. Investigators must submit the following reports to the IRB on a timely and complete basis, together with any additional information specified in the standard IRB form or otherwise requested by the IRB:

a. Status Report (Part VII, Form 2). This report must be submitted no later than the 12th month following the initial review or most recent IRB annual review and reapproval, or more frequently if directed by the IRB. The current informed consent document must be attached. Late submission will result in study SUSPENSION. The IRB will review the information submitted, and determine whether to approve continuation of the study or take other action.

b. Request for Modification (Part VII, Form 3). This form must be submitted whenever changes are made in the protocol or consent document. If the changes are only editorial or grammatical, or do not affect patient risk-benefit, the Investigator should highlight this fact, as the changes may be eligible for expedited review by the IRB Chairperson. The IRB need not review and approve an amended Investigation Brochure unless there have been material changes; the Chairperson may determine whether there have been material changes, and may act for the Board if there are none. The Investigator is responsible to specifically notify the IRB if there are any material changes in the brochure which have not previously been submitted to the IRB. The Request for Modification form will also be used to request REACTIVATION of a study which was previously approved, was suspended for data gathering or other purposes, and is now being proposed for reactivation (do not submit an entirely new protocol request). Modifications may not be implemented in either the protocol or the informed consent document without IRB approval.

c. Protocol Deviations. A protocol deviation is any change or alteration from the procedures set forth in the study protocol. Protocol deviations can be minor (e.g., administrative) or major. Protocol deviations that occur in research shall be submitted to the IRB using a Miscellaneous Report Form. The IRB Chair will review the protocol deviation and determine whether it can be reviewed via an expedited process (by the IRB Chair) or whether it requires full IRB review. All major protocol deviations will be reviewed by the full IRB, with follow-up communication and actions with the Investigator, as determined by the IRB.

d. Adverse Events (Part VII, Form 4). Reporting of adverse events varies depending upon whether the event is classified as "internal" or "external." Health and Human Services regulations (45 CFR 46.103(a) and 46.103(b)(5)) only require reporting of adverse events that are (i) unexpected; (ii) related or possibly

related to participation in the research; and (iii) suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. However, the NMH IRB has determined that *all internal adverse events* will be reviewed by the IRB according to the following procedure:

(1) If the Investigator is engaged in a multi-center clinical trial, an "*internal adverse event"* is one where an adverse event is experienced by subjects enrolled by the Investigator(s) at NMH. In the context of a single-center clinical trial, all adverse events are considered internal adverse events. Upon becoming aware of an internal adverse event, the Investigator must report it promptly to the IRB for review. Further, the Investigator also must ensure that the adverse event is reported to a monitoring entity if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

(2) If the Investigator is engaged in a multi-center clinical trial, an "*external adverse event*" is one where an adverse event is experienced by a subject enrolled by an Investigator at another institution engaged in the clinical trial. External adverse events are not required to be routinely submitted to the IRB for review. The IRB acknowledges that the Sponsor is in a better position to assess the implications and significance of adverse event information from multiple sites and to make a determination about whether an adverse event is an unanticipated problem. Accordingly, the Investigator may rely on the Sponsor to determine which, if any, external adverse events need to be reported to the IRB. For those external adverse events that the Sponsor has determined require a change in protocol or revisions of the informed consent document, such requests shall be forwarded to the Research Department at NMH in the case of Cancer Center studies or, in the case of all other studies, directly forwarded to the IRB Office.

Unless otherwise directed by the Sponsor or the IRB Chairperson, the study may continue pending IRB review of follow-up modifications.

e. Closures (Part VII, Form 5). All study closures must be reported, regardless of the reason for closure. If any subjects will continue through a course of study treatment following closure, or will continue to be monitored for data gathering or other study-related purposes, then continuing status reports to the IRB (usually annually) will be required following closure.

f. Advertisements. All advertisements, bulletins, subject recruitment materials, and public promotions of a study under IRB review which are directed to potential subjects are considered to be an extension of the informed consent process, and must be specifically approved by the IRB before being used. If the referring physician is also an Investigator, any referral letters are considered an extension of the informed consent process and must be submitted to and specifically approved by the IRB before sending.

Advertisements directed to a potential subject's referring physician and other scientists, nurses and administrative staff do not require IRN approval, but may be reviewed by the IRB at the discretion of the IRB Chairperson.

g. Miscellaneous Reports (Part VII, Form 7). Any other communication from Investigators to the IRB may be transmitted via the Miscellaneous Reporting Form.

2. **IRB's Responsibilities.** As part of its monitoring responsibilities, the IRB shall:

a. Investigate all complaints coming to the attention of the IRB regarding the study from patients, family, members of the Medical Staff or others;

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

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

(1) All reports required to be completed by the Investigator and filed with the sponsor, the FDA, HHS and the IRB are being completed and filed;

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

(3) All other documentation required by the IRB is being obtained and maintained by the Investigator;

(4) The conditions, if any, attaching to the IRB's approval or the FDA or HHS approval are being adhered to;

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

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

The IRB may, at any stage of any review, SUSPEND a study pending further review, require MODIFICATIONS or impose CONDITIONS on a continuing study, or REVOKE approval.

3. **IRB Policy on Re-Consenting**. The IRB shall determine, in any case where a report of protocol modification, adverse events, or other information indicates a change in patient risk or benefit, whether the consent document must be changed. If it is determined that the consent document must be changed, and if there are subjects enrolled locally, the IRB's policy on re-consenting shall be that the subjects to be re-consented will be determined based on a review of the protocol and the modifications to the consent document. Subjects determined by this process to require re-consenting will be promptly notified of the material new information, including all newly identified risks, and/or re-consented, as most appropriate in each case. In the case of newly identified, life-threatening risks which are likely related to the study, the IRB may direct that enrolled subjects be re-consented as promptly as reasonably possible. In each case, the decision whether (and how) to notify or re-consent subjects shall be based on the apparent overall best interest of the subjects enrolled and the reasonableness of notification or re-consenting under the circumstances.

4. **Investigator's Responsibility.** (See also, Part VI, Investigator Responsibilities and Standards). The Investigator shall submit timely and complete reports to the IRB as described in Section 1, above. The Investigator is responsible for notifying the IRB whenever approval of the study or Investigator is withdrawn by the sponsor, FDA, or HHS. Additionally, the Investigator shall notify the IRB in the event that the Investigator discontinues the study at any time other than the scheduled completion date, or in the event there are any unanticipated problems involving risks to human subjects, or variances from the approved protocol, the federal regulations or the conditions established by the IRB. In the event that the FDA releases a device or drug which is the subject of a study, from its designation as an investigational device or drug, or the study is otherwise released from coverage of the federal regulations, the Investigator shall so notify the IRB Chairperson and shall provide documentation indicating such release to the satisfaction of the IRB Chairperson. At the conclusion of any study or upon FDA or HHS release, the IRB may require such follow-up information and documentation of a completed or discontinued study as it may determine appropriate.

V.
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 which

meet the federal regulatory requirements are generally expected by the IRB, even for studies which 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 (8th grade level is often recommended as a benchmark). Informed consent may be obtained by the Investigator or research nurse. For registry studies only, the Investigator may delegate authority to obtain informed consent to a data coordinator or other designated member of his/her staff provided that such individual has received training in informed consent procedures.

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, research nurse or data coordinator 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, research nurse or data coordinator 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 research nurse or data coordinator 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, research nurse or data coordinator should explain to the subject his or her rights as a research participant. 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, research nurse or data coordinator 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, research nurse or data coordinator has determined that the prospective subject (or representative) has sufficient knowledge and comprehension of each element of consent, the subject (or representative) should read (or have read to him or her) and voluntarily sign and date the informed consent document. The Investigator or authorized staff should sign and date 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.

To the greatest extent possible, the informed consent process should be conducted in person and not over the telephone. However, when geographic distances between the subject and the research site are significant and a face-to-face discussion can not reasonably be arranged, conducting the process over the telephone may be considered. Use of telephone consent is always subject to the requirement that the consent process must be understandable and meaningful to the subject and must result in true informed consent. Some subjects may have language, speech, hearing or other communication issues that make telephone consent impossible. Other technologies, such as Skype, may be used to enhance the telephone process when available.

When telephone consent is used, written consent may be obtained using a mailed, faxed, or scanned and e-mailed consent document. In such cases, 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 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 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 NMH IRB and the approval date(s), and to identify the Study Sponsor. The individual being asked to participate should be referred to as the "subject," not as the "patient" or "participant" or by any other term which 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 which 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)."

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 will the informed consent process.

D. ELEMENTS OF INFORMED CONSENT

Federal regulations define the following elements of a complete informed consent document. It is recommended that these elements 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 invitation to participate in a research study. The term "experimental" may be used and is

encouraged. 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. **Eligibility.** The consent document should describe briefly, why the prospective subject is eligible to participate (e.g., inclusion criteria such as a specific disease, condition, characteristic, background). When appropriate, the approximate number of subjects that will be involved in the study should be stated. When appropriate, criteria for subject exclusion should be stated (e.g., pregnancy, age limitations, health restrictions).

4. **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 scientific purpose and objectives of the research, which should help the subject assess the importance of the study relative to individual values. When appropriate, this statement should include not only the immediate purpose of the study, but also any larger, ultimate purpose. If there are primary (e.g., to evaluate toxicity) and secondary (e.g., to evaluate possible benefit) purposes, they should be separately identified, clearly enough that the patient is not misled about issues of risk and benefit. The statement of purpose must not understate the experimental nature of the research, understate the purpose of determining drug toxicity or other risks, or mislead the subject into believing that there is more therapeutic potential than known. This section should also include the expected duration of the subject's participation in the study

The purpose of the study statement should also include the FDA status of any study drugs or medical devices (e.g., Drug A is an investigational drug while Drug B is FDA approved for this use).

5. **Study Procedures**. This section of the consent document explains the study procedures and should include the following:

a. A description of the study design (e.g., longitudinal, single-blind, double-blind, placebo), method of subject assignment to groups (e.g., randomization) and probability of assignment (e.g., 50-50 chance). Despite the fact that subjects may be kept unaware of treatment assignments in blinded studies and research involving placebos, subjects must be made aware of all the possible interventions and the method of assignment. Naturally, the description of the study design and method of subject assignment must be simplified.

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.

6. **Possible Risks and Discomforts**. The consent document should fully disclose all known or reasonably anticipated 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 (e.g., aspirin: dizziness, ringing in the ears, bleeding inside the stomach, etc.). Risks should not be understated or overstated. In some cases it is considered desirable to cite statistical probability of risk occurrence, risk prevention measures, reversibility and treatment, but this should be done very cautiously since any statistical values or other qualifiers (e.g., "likely," "rare") must be current when used and then must be updated if and when they change.

The terms "minimal risk," "greater than minimal risk" and "significant risk" generally should not be used in the consent document. A research subject is not likely to understand the meaning of these terms.

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

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 on 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 on 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 on this study, you must tell your study doctor immediately.

7. **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 non-therapeutic 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.

8. **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.

9. **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 other third-party payor. If the sponsor or another source is providing free study drugs or paying other costs, this should be stated, but with care to ensure that the subject is not misled into believing that other costs (e.g., physician and hospital care) will be covered. The consent document should clearly delineate the costs covered by the study sponsor and those which will be billed to the subject's insurer and may become the financial responsibility of the subject, if denied. For example:

[Sponsor] will cover the cost of the treatment, procedures and tests listed in this consent document and required by the study but which are not the "standard of care" for your medical condition, rather than a part of the investigational research. "Standard of care" means medical care that you would be likely to receive whether or not you participated in the study. If you have health insurance, the charges for items and services that are part of the standard of care will be billed to your insurance company(s) and may be covered . If not covered, these charges will be your personal financial responsibility. The items and services that are part of this study that are not considered to be standard of care and which will be provided at no charge as part of the study are:

[List]

10. **Compensation for Participating/Financial Interests**. 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.

The nature, amount and method of payment of financial or other compensation must not constitute undue inducement of the subject (e.g., the compensation alone should not serve as sufficient inducement for the subject to volunteer). When establishing the amount and type of compensation, the Investigator should consider the background and socioeconomic status of the subject population.

If no compensation will be paid, this should be stated.

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.

11. **Injury and Emergency**. The consent document should 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.

If a commercial sponsor has agreed to provide compensation in case of injury to research subjects, the extent and limitations of the compensation should be stated carefully.

12. **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, NMH, the NMH IRB, the FDA and/or HHS, and the study sponsor (identified by name).

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.

13. **Rights as a Research Participant**. This section of the consent document should contain essentially the following language:

If you have any questions about your rights as a research participant, you may contact NMH's Institutional Review Board, a group of people who are responsible to protect the rights of research subjects, by calling 402-354-4035.

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

> Your participation in this research is voluntary. You can decide not to participate in this study or you can withdraw from this study at any time. Your decision will not result in any loss of benefits to which you are entitled. If any new information develops during the course of this study that may affect your willingness to continue participating, you will be informed.
>
> If you decide to withdraw, you should discuss your decision with your doctor first. Your doctor may terminate your participation in this study if he or she deems that doing so is in your best medical interest, and it is possible that this study will be discontinued before your participation in it is concluded.

15. **Documentation of Informed Consent**. This section of the consent document should contain essentially the following language:

You are voluntarily making a decision whether to participate in this research. Your signature means that you have read and understood the information presented and decided to participate. Your signature also means that the information on this consent document has been fully explained to you and any questions you asked have been answered to your satisfaction. If you think of any additional questions during the study, you should contact the Investigator(s). You will be given a copy of this consent document.

16. **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/Signature of Subject's Personal Representative
_____		_____
Authority of Personal Representative if signing on behalf of Subject		Printed Name of Subject / Subject's Personal Representative
_____	_____	_____
Date	Time	Signature of Person Conducting Informed Consent Discussion
		_____
		Printed Name of Person Conducting Informed Consent Discussion

17. **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. 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 1-7, and the concluding assent statement, must be included.

F. CONSENT TO USE TISSUE OR RECORDS FOLLOWING DEATH

Research subjects will sometimes give informed consent and HIPAA authorization to use their blood, tissue, other samples and/or records for current or future research, either as their sole means of participating in a research study or ancillary to a therapeutic study in which they are participating. This includes but is not limited to secondary site studies where the only activity at NMH is the transmittal of blood, tissue, other samples or records to the research institution. Unless the informed consent or authorization document expressly states that it expires upon death, the consent/authorization will survive death and the use of the subject's blood, tissue, other samples or records may continue following death without further consent, unless and until (i) an event of expiration listed in the consent or authorization document occurs (e.g., the end of the research study), or (ii) the subject's legally authorized representative expressly revokes the consent/authorization.

All requests for access to stored tissue for research purposes require approval by the IRB. The Methodist Health System Privacy/Security Committee has delegated its authority to review any privacy matters related to research proposals involving access to stored tissue to the IRB. The NMH policy regarding access to stored tissue for research is included at Appendix A.

G. WAIVERS OF CONSENT OR AUTHORIZATION

Under certain rare circumstances, the IRB may grant a waiver of the requirement of informed consent or 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. This waiver or alteration may not be granted by the Chairperson on an expedited basis. A Completed Request for Waiver form must be submitted in addition to a completed Request for Review form. (See Part VII, Forms 1 and 6) The regulatory standards for a waiver are:

1. **Waiver of Informed Consent**. The IRB must find that:

a. The research involves no more than minimal risk to the subjects.

b. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

c. The research could not practicably be carried out without the waiver or alteration.

d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

2. **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:

(1) There is an adequate plan to protect individual identifiers from use and disclosure.

(2) 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.

(3) 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.

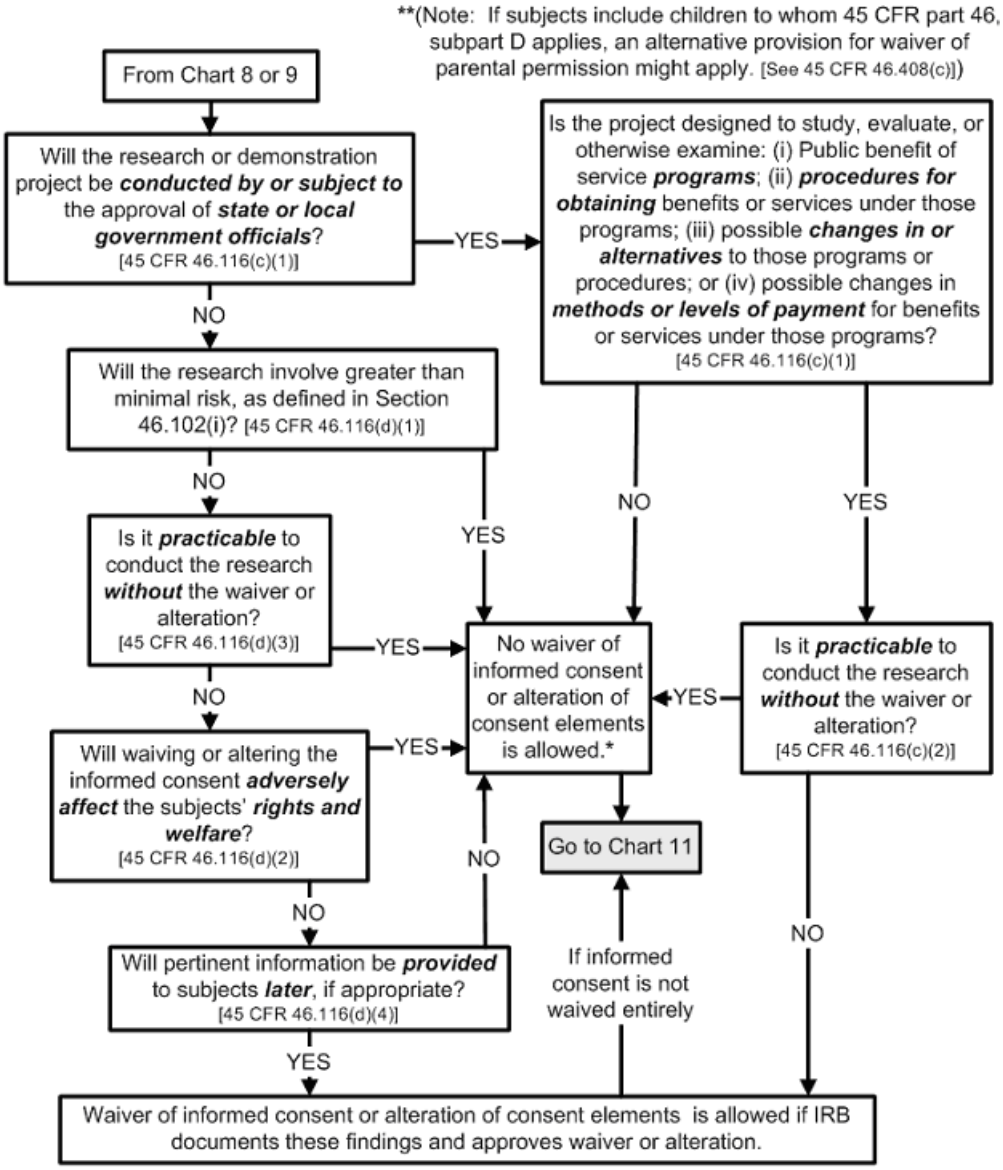
See OHRP Decision Charts 10-11, on the following pages, for analysis of potential waivers of informed consent.

H. 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 certain research on decedents' information. Researchers planning to use PHI at NMH for any of these purposes without individual authorization should first contact NMH'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.

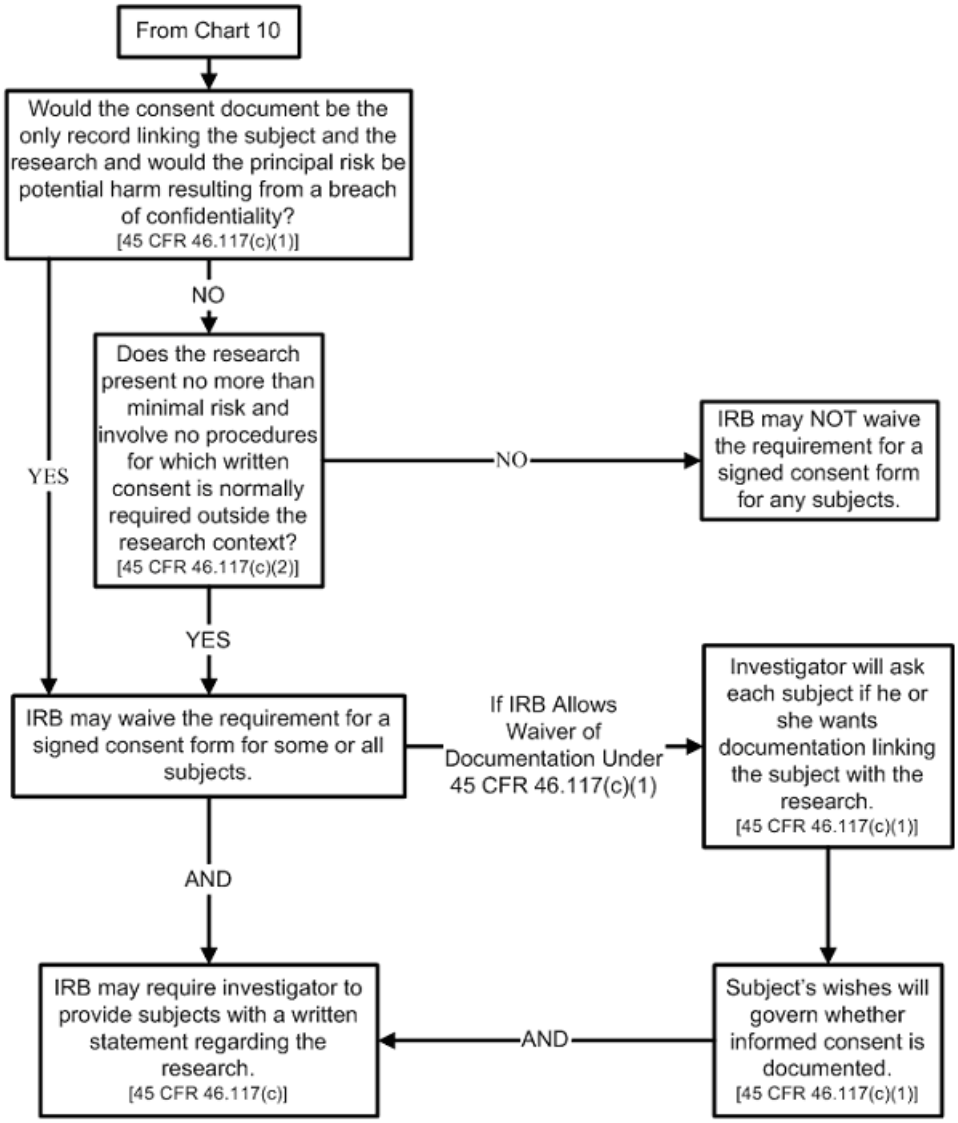
Chart 10: Can Informed Consent Be Waived or Consent Elements Be Altered Under 45 CFR 46.116(c) or (d)?**



* Note: See OHRP guidance on informed consent requirements in emergency research at http://www.hhs.gov/ohrp/policy/index.html#emergency for further information on emergency research informed consent waiver.

September 24, 2004

Chart 11: Can Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?



September 24, 2004

--SAMPLE--

WHAT ABOUT CONFIDENTIALITY?

Authorization for Use and Disclosure of Information

Use of your personal health information is critical to the success of this research study. However, efforts will be made to protect the confidentiality of your personal health information consistent with federal privacy laws.

All or part of your medical records, along with the records of all other patients participating in this study from this and other institutions will be sent to the **[Sponsor/Study Group(s) Name(s)] in [City and State]** as well as to the **[Other Related Recipient(s), such as Statistical Reviewer(s), Etc.]**, in **[City/State]** to be reviewed and analyzed by physicians and other study personnel.

For purposes of quality assurance, data analysis and research oversight, your personal information may also be disclosed to qualified representatives of NMH, NMH's Institutional Review Board, the Food and Drug Administration (FDA), officials of the Department of Health and Human Services, other research oversight bodies, and other entities who are directly participating in, monitoring, or supporting this research. These entities may see information that specifically identifies you. All of these entities, however, are committed to protecting the confidentiality of your information.

The exact information that will be used and disclosed will vary depending upon your treatment, but may include name, age, sex, diagnosis, medical history, lab tests, x-ray reports, type of treatment, your response to treatment, and any other information about you or your medical care contained in your hospital records, doctors' office records, laboratory, operating room and other records.

By signing below, you authorize the study doctors to use your information described above in the course of this research study and to disclose your information to the entities listed above at any time. Once disclosed, your information may be subject to redisclosure and no longer protected by federal privacy laws.

You may choose not to sign this authorization for use and disclosure of your information. However, if you choose not to sign this authorization, you will not be eligible to participate in the research study. The reason for this is because the success of the research study depends upon use of the information we collect in the course of the study. A decision not to sign this authorization and not participate in the research study will not affect your ability to continue regular treatment with your doctor.

If you sign this document, your authorization is valid indefinitely and has no termination date. However, you may revoke this authorization at any time, without penalty, by voluntarily withdrawing from the research study, The researchers will no longer use or disclose your personal information for this research, except to the extent they have taken action in reliance on your prior authorization.

You have a right to inspect and copy your personal information that is being used and disclosed by the research study doctors to the extent permitted by federal privacy laws. However, if you are enrolled in a study which includes treatment, and if your access to any study information would be inconsistent with or interfere with the study protocol, your right of access to some or all of the information may be suspended without further notice to you, while the research is in progress; your right of access would then be reinstated upon conclusion of the research.

****

I authorize the research Investigators to use and disclose my information as explained above. I certify that I have received a copy of this authorization.

_____	_____	_____
Date	Time	Subject's Signature/Signature of Subject's Personal Representative
_____		_____
Authority of Personal Representative if signing on behalf of Subject		Printed Name of Subject / Subject's Personal Representative
_____	_____	_____
Date	Time	Signature of Person Conducting Informed Consent Discussion
		_____
		Printed Name of Person Conducting Informed Consent Discussion

VI.
INVESTIGATOR
RESPONSIBILITIES, STANDARDS AND CORRECTIVE ACTION

RESPONSIBILITIES AND STANDARDS

Investigators participating in research studies under the approval of NMH'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 Manager will monitor Investigator's compliance under this Part VI and report deficiencies to the IRB Chair.

A. CREDENTIALS

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

2. Maintain Medical Staff membership and clinical privileges as necessary to participate in the study at NMH.

3. Notify NMH's Medical Staff office 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 and/or the FDA.

B. IRB – RELATED TRAINING

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

2. Complete the current on-line IRB training course approved by the IRB and provide documentation of successful completion to the IRB Manager prior to the Investigator's submission of his or her first Request for Study Approval with the NMH IRB. The costs of registration will be paid by NMH. Investigators who have completed IRB training at a different institution can satisfy this requirement by providing documentation of successful completion of a training course to the IRB Manager.

3. Every 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.

4. Cooperate in any other reasonable request by the NMH 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 (See Part IV, How Studies Are Submitted and Reviewed).

2. Complete on a timely basis all required reports to the study sponsor, the FDA, or other regulating authorities.

3. Immediately notify the IRB, through NMH Medical Staff office, 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, 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 from the Sponsor or other sources to the Investigator participating in the research; and any significant financial interest the Investigator has in the research study. The NMH 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:
>
> - 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.
>
> - 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.
>
> - 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.
>
> - 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.
>
> - 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.

6. Assure that charges for products and services rendered in the course of the research study are properly billed, including assurance that (i) charges to the subject are consistent with the representations made during the informed consent process, (ii) charges to Medicare, Medicaid or insurers are limited to permitted/non-excluded charges, and (iii) charges are not duplicate-billed to the subject and a third-party payor or to multiple third-party payors or grant agencies.

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, the FDA, or HHS, and notify the IRB promptly in the event any such audit or investigation is initiated.

G. INVESTIGATOR AGREEMENT

Execute and return the NMH IRB Investigator Agreement which is included at the end of this Part of the Handbook.

CORRECTIVE ACTION

By submitting a request for approval to participate as an Investigator in a research study, and by participating, an Investigator accepts and agrees to abide by all of the terms, conditions and standards set forth in this IRB Handbook, as well as all applicable laws and regulations, and Sponsor requirements. In the event an Investigator fails to do so, the NMH IRB will have the authority, and the responsibility, to take any corrective action appropriate to the circumstances. In doing so, and subject to the IRB's discretion to vary from these guidelines in any case as warranted by the circumstances, the IRB will generally adhere to the following principles:

A. DELINQUENT REPORTS

Failure to submit annual reports or other required periodic reports to the IRB on a timely and complete basis, or failure to respond on a timely and complete basis to an IRB request for information, will result in study suspension pending proper submission of the

required information and acceptance by the IRB. Continued failure will result in revocation of authority to participate as an Investigator in the study.

B. OTHER VIOLATIONS

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

1. Suspension of the Investigator's authority to participate in the research study. This may be most appropriate, for example, in the case of a failure to submit required information, temporary suspension of medical staff privileges, temporary disability, unresolved problems in the Investigator-sponsor relationship, or other circumstances which appear amenable to correction in the foreseeable future. The entire study at NMH may be suspended, unless there are other Investigators who can properly manage the study and are not subject to the same corrective action and the study sponsor approves.

2. Imposition of additional reporting or monitoring requirements. This may be most appropriate, for example, in the case of an Investigator coming off suspension; or other violations where the Investigator has provided reasonable assurances of corrective measures and the IRB determines that a period of additional reporting or monitoring is warranted. Monitoring may include, but is not limited to, additional reporting by the Investigator, on-site audits of the Investigator's research records, or auditing of the informed consent process.

3. Revocation of the Investigator's authority to participate in the research study (and possibly other future studies) at NMH. This may be most appropriate, for example, in the case of continuing problems which are not resolved through dialogue and cooperation; or serious violations such as failure to obtain proper informed consent, failure to report significant adverse events, protocol violations, significant financial conflicts of interest which are not approved by the IRB, or other violations which jeopardize subject rights, health or welfare.

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

C. PROCEDURES

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

IRB may be requested in writing; the IRB shall have sole discretion to determine whether or not to entertain an appeal and, if so, by what procedures.

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board

Investigator Agreement

Name of Institution: The Nebraska Methodist Hospital

Applicable Federalwide Assurance (FWA) #: FWA00003377

Investigator's Name: _____

(1) The Investigator named above has reviewed The Nebraska Methodist Hospital Institutional Review Board *Handbook for IRB Members and Investigators*, including The *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, and all of the relevant institutional policies, procedures and Investigator responsibilities and standards described therein.

(2) The Investigator understands and hereby accepts the responsibility to comply with the standards and requirements stipulated in the above documents and to protect the rights and welfare of human subjects involved in research conducted under this Agreement.

(3) The Investigator will comply with all applicable National, State, or local laws or regulations that may provide additional protection for human subjects.

(4) The Investigator will abide by all determinations of the IRB designated under the above Assurance and will accept the final authority and decisions of the IRB, including but not limited to directives to terminate participation in designated research activities.

(5) The Investigator will complete any educational training required by the Institution and/or the IRB prior to initiating research covered under this Agreement or within other time frames designated by the IRB.

(6) The Investigator will report promptly to the IRB any proposed changes in the research conducted under this Agreement. The Investigator will not initiate changes in the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.

(7) The Investigator will report immediately to the IRB any unanticipated problems involving risks to subjects or others in research covered under this Agreement.

(8) The Investigator will obtain, document, and maintain records of informed consent from each subject or the subject's legally authorized representative as required under DHHS

and FDA regulations (or other international or national equivalent) and stipulated by the IRB.

(9) The Investigator acknowledges and agrees to cooperate in the IRB's responsibility for initial and continuing review, record keeping, reporting, and certification. The Investigator will provide all information requested by the IRB in a timely fashion.

(10) In conducting research involving FDA-regulated products, the Investigator will comply with all applicable FDA regulations and fulfill all Investigator responsibilities (or Investigator-sponsor responsibilities, where appropriate), including those described at 21 CFR 312 and 812.

(11) The Investigator will not enroll subjects in research under this Agreement prior to its review and approval by the IRB.

(12) Emergency medical care may be delivered without IRB review and approval to the extent permitted under applicable Federal regulations and State law. However, data and information obtained as a result of emergency medical care may not be included as part of federally-supported or –conducted research.

(13) This Agreement does not preclude the Investigator from taking part in research not covered by the Agreement.

(14) The Investigator acknowledges that he/she is primarily responsible for safeguarding the rights and welfare of each research subject, and that the subject's rights and welfare must take precedence over the goals and requirements of the research.

Investigator Signature: _____ Date _____

Name: _____
(*Last*) (*First*) *(Middle Initial)*
Address: _____ phone #: _____

_____
(*City*) (*State/Province*) (*Zip/Country*)

FWA Institutional Official (or Designee): _____ Date _____

Name: _____ Institutional Title: _____
(*Last*) (*First*) (*Middle Initial*)

Address: _____ phone #: _____

_____
(*City*) (*State/Province*) (*Zip/Country*)

VII.
FORMS

METHODIST HOSPITAL

FORM 1

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board
Request for Review
of Investigational Study

Use of Form: This form is to be used by the Principal Investigator to request initial review and approval of a proposed study involving human subjects. This form should not be used for annual or other periodic status reports of previously approved studies, unless approval for a modification is requested. This form must be completed, with attachments, and submitted to the Medical Staff Manager.

1. **Title of Study:**

2. **Date of this Request:**

3. **Medical Staff Department:**

4. **Principal Investigator's Name:**
   Office Address:
   Office Phone:

5. **Secondary Investigator(s):**

6. **Sponsor/Manufacturer Name:**
   Address:
   Contact Person:
   Telephone:

7. **Reason for Request (Check All Which Apply):**
   - ☐ Federally Sponsored Human Research
   - ☐ Investigational Drug Under FDA Supervision
   - ☐ Investigational Device Under FDA Supervision
   - ☐ Intraocular Lens Classified Investigational by FDA
   - ☐ IRB Review Required by Sponsor/Manufacturer
   - ☐ Modification of Previously Approved Study
   - ☐ Other (Explain): _____

8. **Study Will Be Conducted:**
   - ☐ Wholly or Partially at Methodist Hospital
   - ☐ Entirely Off Methodist Hospital Campus

9. **Check All Special/Vulnerable Groups Within Subject Population:**

☐ Children (Ages: _____)	☐ Physically Disabled
☐ Pregnant Women	☐ Mentally/Emotionally Disabled
☐ Fetuses	☐ Other (Describe: _____

Please provide summary statements addressing the following points. Although this information may be contained in the other documents you submit, your summaries here will help assure prompt and informed IRB action. If you are seeking only to modify a previously approved study, you may simply describe the changes (or "no change") in each category.

10. **Nature and Purpose of the Study:**

11. **Characteristics of Subject Population** (Number, Age Ranges, Gender, Ethnic Background, and Health Status; Criteria for Inclusion and Exclusion, and Justification for the Utilization of Any Special/Vulnerable Groups):

12. **Method of Subject Selection** (Methods to be Employed in the Identification/Recruitment of Potential Subjects):

13. **Risks to the Subjects** (Potential Risks; Probability, Severity, Potential Duration and Reversibility of Such Risks):

14. **Protection Against Risks** (Procedures to be Utilized to Prevent/Minimize Any Potential Risks):

15. **Benefits** (Potential Benefits To Be Gained By the Subject as Well as Benefits That May Accrue to Medical Science or Society in General):

16. **Risk-Benefit Analysis** (Why the Risks to the Subject are Reasonable in Relation to the Anticipated benefits to the Subject and/or in Relation to the Importance of the Knowledge that May Reasonably be Expected to Result): See above.

17. **Therapeutic Alternatives** (Therapeutic Alternatives That May Be Advantageous to the Subject):

18. **Informed Consent:** Please describe the process by which you will obtain the informed consent of each study subject, addressing (i) who conducts the main consent discussion with the subject, (ii) when this discussion takes place, (iii) who is present at this discussion and what materials are presented to the subject, (iv) when the subject is asked to sign the consent document, (v) whether the subject is provided a copy of the consent document, (vi) whether you anticipate ever enrolling a subject with surrogate consent because the subject is not competent to consent for himself or herself, and (vii) any circumstances under which you might enroll a subject without informed consent.

19. **Documentation:** The following documents are submitted with this Request for Review (If No, explain why not and where/when the document(s) will be available):

☐ Yes	☐ No	Complete Investigational Plan and Protocol	
☐ Yes	☐ No	Report of Prior Investigations	
☐ Yes	☐ No	Patient Informed Consent Form	
☐ Yes	☐ No	Reporting Forms That the Sponsor Requires from IRB	
☐ Yes	☐ No	Medical Staff Department Recommendation	
		☐ Yes ☐ No (Secondary Investigations): Certification of Review and Approval by the Primary IRB	
☐ Yes	☐ No	Fee **** (see page 4)	
☐ Yes	☐ No	Other (Describe): _____	

20. **Financial Considerations:**
    a. Do you or any other local investigators have any financial or management interest in the sponsor or manufacturer, direct or indirect, in any form? ☐ No ☐ Yes, as Follows:

    b. Will there be any payments from the study sponsor, study group or other interested party to you, your staff or your institution in connection with this study, whether designated for fees, expenses, or otherwise?

    ☐ No ☐ Yes, As Follows (Please provide an itemization of all anticipated payments, and how they will be used or applied. A study budget should be provided if available):

    c. Will there be any costs or charges to the patients in this study, beyond what they would incur from standard or alternative therapies? ☐ No ☐ Yes, as Follows (Including Expected Source of Payment):

21. **Research/Investigator Status:**

    a. Has the proposed study, or any substantially similar study, previously been denied approval or had its approval suspended or revoked by this IRB or any other IRB? ☐ No ☐ Yes (explain):

b. Have you (or to the best of your knowledge, any secondary investigator) ever been subject to any of the following (or is any formal investigation or other formal action pending which could lead to such a result):

- Revocation of approval to serve as an investigator in a research study, imposed by any IRB, sponsor or other entity? ☐ No ☐ Yes (explain):

- Debarment as a government contractor, or disqualification from any government or private grants or research programs? ☐ No ☐ Yes (explain):

- Criminal prosecution or civil lawsuit seeking criminal penalties, injunction or damages arising out of clinical research involving human subjects? ☐ No ☐ Yes (explain):

c. Do you agree to notify the IRB chair if events occur which would change any of your answers to the preceding questions? ☐ No ☐ Yes

d. Have you received, and do you agree to review, understand and be bound by, this IRB Handbook? ☐ No ☐ Yes

Investigator's Certification: I certify that the foregoing is complete and accurate to the best of my knowledge. I will advise the Chair of the IRB of any significant changes of which I become aware. I have received, read and understand the Handbook for IRB Members and Investigators, including the Statement of Ethical Principles and Policy, and agree to comply with all of the terms, conditions and standards contained within the Handbook, with all periodic reporting requirements, and with all applicable laws and regulations.

Signature of Principal Investigator: _____

Date Submitted: _____

****Please note: The Methodist Hospital IRB Guidelines require a one-time fee of $2000.00 for submission of new protocols. This fee applies to industry-sponsored studies, not nonprofit cooperative research group trials or local physician-investigators. The fee is due upon submission of the Request for Review.

METHODIST HOSPITAL

FORM 2

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board
Investigator's Status Report

Use of Form: This form is to be used by the Principal Investigator of a study previously approved by the IRB, to report on the status of the study. Periodic reports (at intervals established by the IRB, but no less than once per year) are required by law and as a condition to continuing approval of the study.

1. **Title of Study:** _____

   _____

   _____

2. **Principal Investigator's Name:** _____

3. **Date of this Report:** _____

4. **Date of Original Methodist IRB Approval:** _____

5. **Number of Subjects in Study, to Date:** _____

   Locally (under NMH IRB Jurisdiction): _____

   Nationally (if known, or estimate): _____

6. **What is the current status of this study (check one):**

   a. ☐ Open to accrual of additional subjects (check this box even if accruals are temporarily suspended)

   b. ☐ Closed to accruals, some subjects still being treated under the study (requires annual reporting)

   c. ☐ Closed to accruals, no subjects still in treatment, data gathering still ongoing (requires annual reporting)

      Date of Closure _____

      Reason for closure _____

7. **If you checked 6a or 6b:**

   a. Is there any reason to believe the potential risks or benefits are materially different than believed at the time this study was last reviewed by this IRB?

      ☐ No

☐ Yes (explain): _____

_____

b. Has this IRB received all known safety/adverse event reports on this study?

☐ No (explain): _____

_____

☐ Yes

c. **Have any significant new alternative treatments become available, which should be brought to the study subjects' attention?**

☐ No

☐ Yes (explain): _____

_____

d. **Have there been any modifications to this study, which have not been reviewed and approved by this IRB?**

☐ No

☐ Yes (explain): _____

_____

8. **Financial Interests.** (This paragraph does not need to be completed more than one time per year for any study group sponsoring multiple studies with the same financial considerations.)

a. Please detail below, all forms of payment which you or any member of your practice group receives from the Sponsor (or from any other source excluding normal reimbursement for professional medical services) in connection with this study, and how those funds are applied:

Funds received (including amounts): _____

_____

Application of funds: _____

_____

b. Please see Section VI.E of the IRB Handbook. Do you or any other investigators have any significant financial interests as defined in that Section? ☐ Yes ☐ No (explain):

_____

_____

9. **Other – Please Provide Any Other Information Which May Be Helpful to the IRB's Review of this Study:**

_____

_____

10. **PLEASE ATTACH A COPY OF THE CURRENT INFORMED CONSENT FORM.**

BY SIGNING THIS FORM, YOU CERTIFY THAT INFORMED CONSENT HAS BEEN OBTAINED AND WILL BE OBTAINED FROM EVERY STUDY SUBJECT, AND THAT THE INFORMED CONSENT PROCESS WILL BE FOLLOWED, IN COMPLIANCE WITH LEGAL AND REGULATORY STANDARDS AND THE STANDARDS SET FORTH IN THE METHODIST IRB HANDBOOK.

Signature of Principal Investigator: _____

Date Submitted: _____

METHODIST HOSPITAL

FORM 3

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board Request for Modification of Investigational Study

Use of Form: This form is to be used by the Principal Investigator of a study previously approved by the IRB, to request IRB approval of a change in protocol, change in consent form, or other study modification.

1. Title of Study:

2. Principal Investigator's Name:

3. Date of this Request:

4. Date of Original Methodist IRB Approval: ☐ **Open** ☐ **Closed to Accrual**

5. Number of Subjects Enrolled Locally:

6. Summary of Modifications Requested:

(a) Study modification:

Administrative change
Accrual
Eligibility criteria
Status Change: Suspension Reactivation
Recruitment/educational materials
Informational Report
Study treatment or procedure
Confidentiality
Risks

(b) Method of review allowed:

Expedited
Full board

(c) Summary of consent form changes, and reasons for changes:
Reconsent Required YES NO

7. Will the proposed changes materially affect the risk/benefit analysis?

☐ No ☐ Yes Please explain:

8. Will the proposed changes increase the patient's cost to participate in the study?

☐ No ☐ Yes Please explain:

9. Are the following documents attached to this request?

☐ Yes ☐ No **Protocol modification / revised protocol**
☐ Yes ☐ No **Revised consent form**
☐ Yes ☐ No **Other supporting documents (list)**

Signature of Principal Investigator: _____
Date Submitted: _____

METHODIST HOSPITAL

FORM 4

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board
Adverse Event/Safety Reports

Use of Form: This form is to be used by the principal investigator of a study previously approved by the IRB, to report to the IRB when an adverse event report or safety report has been issued regarding the study.

BEFORE SUBMITTING THIS FORM, THE SUBMITTING INVESTIGATOR MUST REVIEW THE ADVERSE EVENT REPORT, AND CERTIFY THAT IT FALLS WITHIN ONE OF THE FOLLOWING THREE CATEGORIES (check ONE):

☐ **This is a report of an internal adverse event (an adverse event occurring at Methodist Hospital).**

☐ **The report meets all of the following criteria:**

- **This is an OPEN study at Methodist Hospital or it has been closed less than 30 days, or there are still subjects receiving therapy at Methodist Hospital; and**
- **The adverse event reported is unexpected or occurring at an unexpected frequency; and**
- **The adverse event reported is serious; and**
- **The sponsor and the submitting investigator assess the adverse event as probably or definitely related to the study drug in question.**

☐ **The report does not meet the criteria outlined above.**

IF THE LAST BOX IS CHECKED, THE REPORT WILL BE MAINTAINED ON FILE BY THE IRB OFFICE BUT WILL NOT BE SUBSTANTIVELY REVIEWED BY THE IRB.

1. **Title of Study:**

2. **Principal Investigator's Name**:

3. **Date of this Report:**

4. **Number of Subjects in Study, to Date:**

   Locally (under NMH IRB Authority):

   Nationally (if known, or estimate):

5. Date(s) of Adverse Event/Safety Reports:

6. Does the Report Change the Risk - Benefits Ratio for the Subjects? □ No □ Yes If so, How

7. Do You Recommend Changes to the Informed Consent Form? □ No □ Yes If so, Explain:

8. Do You Recommend That Currently Enrolled Subjects be Contacted With Information Regarding These Reports? □ No □ Yes If so, What is Your Plan to Contact Them?

9. PLEASE ATTACH COPIES OF THE ADVERSE EVENT/SAFETY REPORT(S) AND THE CURRENT INFORMED CONSENT FORM.

Signature of Principal Investigator: _____

Date Submitted: _____

METHODIST HOSPITAL

FORM 5

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board
Report of Study Closure
(Two Versions - Closed to Accrual and Permanently Closed)

Use of Form: This form is to be used by the principal investigator of a study previously approved by the IRB, to report to the IRB when the study is being permanently closed to further patient accruals. Do not use this form for routine temporary suspensions of accruals.

1. **Title of Study:**

2. **Principal Investigator's Name:**

3. **Date of this Report:**

4. **Date of Closure:**

5. **Reason for Closure:**

6. **Number of subjects enrolled locally:**

7. **Are there any subjects enrolled locally who:**

   Are still receiving study treatment _____ Yes _____ No

   Are still being followed for study Data or analysis _____ Yes _____ No

Signature of Principal Investigator: _____

Date Submitted: _____

METHODIST HOSPITAL

FORM 6

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board
Request for Waiver of Consent and/or HIPAA Authorization

Use of Form: This form is to be used by the Principal Investigator of a study, to request that the IRB waive (1) some or all of the requirements of informed consent, and (2) individual authorization for use or disclosure of Protected Health Information (PHI) under HIPAA privacy regulations. Waivers should be requested, and will be granted, **rarely**, and only if all of the criteria described in this form are clearly met. Before submitting this form, the Investigator should carefully study Tab V, Informed Consent and Privacy, in The Nebraska Methodist Hospital *Handbook for IRB Members and Investigators*.

This form should be submitted in addition to the separate form entitled Request for Review of Investigational Study.

1. Title of Study:

2. Principal Investigator's Name:

3. Date of this Request:

4. Specify nature of request (check all which apply):

☐ **Alteration of some or all elements of informed consent (if alterations, specify):**

☐ **Waiver of informed consent requirement**

☐ **Waiver of Authorization for Use and Disclosure of Information (HIPAA waiver)**

5. <u>Consent Waiver or Alteration</u>. By requesting an alteration or waiver of informed consent, you are certifying that each of the following elements will be met, and for each element, must provide a detailed explanation:

a. I certify that the research involves no more than minimal risk to the subjects. (Explain all risks and why they are no more than minimal):

b. I certify that the waiver or alteration will not adversely affect the rights and welfare of the subjects. (Explanation):

c. I certify that the research could not practicably be carried out without the waiver or alteration. (Explanation):

d. I certify that whenever appropriate, the subjects will be provided with additional pertinent information after participation. (State whether or not this will be appropriate, and explain):

6. **<u>HIPAA Waiver</u>. By requesting a waiver of authorization for use and disclosure of information (HIPAA waiver), you are certifying that each of the following elements will be met, and for each element, must provide a detailed explanation:**

a. **I certify that this study will involve no more than minimal risk to the privacy of individuals, including each of the following:**

(i) **I have an adequate plan to protect individual identifiers from use and disclosure. (Describe the plan):**

(ii) **I have 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. (Describe the plan, or the basis for any exceptions):**

(iii) **I assure that 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. (Explain in detail):**

b. **I certify that the research could not practicably be conducted without the waiver of individual authorization. (Explanation):**

c. I certify that the research could not practicably be conducted without access to and use of PHI. (Explanation):

d. I certify that the PHI being accessed and used is the minimally necessary PHI for the research purposes. (Explanation):

Investigator's Certification: I certify that the foregoing is complete and accurate. I will advise the IRB Chairperson if there are any changes.

Signature of Principal Investigator: _____

Date Submitted: _____

METHODIST HOSPITAL

FORM 7

THE NEBRASKA METHODIST HOSPITAL 8303 DODGE STREET OMAHA, NEBRASKA 68114 402-354-4000

Institutional Review Board
Miscellaneous Report Form

Use of Form: This form is to be used by the principal investigator of a study previously approved by the IRB, to report to the IRB protocol deviations, reports from data safety monitoring reports, investigator brochures, etc.

Do not use this form for adverse event reporting, modifications, renewals or closures.

1. Title of Study:

2. Principal Investigator's Name:

3. Date of this Request:

4. Summary of report: (attached applicable documents)

Signature of Principal Investigator: _____
Date Submitted:

APPENDIX A

METHODIST HOSPITAL

An Affiliate of Methodist Health System

POLICY AND PROCEDURES

SUBJECT:	Access to Stored Tissue for Research Purposes	**Page 1 of 2**
EFFECTIVE DATE:	3/11	
REVIEWED/REVISED:		
PURPOSE:	Define the process to access stored tissue for research purposes	

POLICY: Requests for access to stored tissue for research purposes require protocol approval by the Methodist Hospital Institutional Review Board (IRB). The Methodist Health System Privacy/Security Committee has delegated its authority to review any privacy matters to the Methodist Hospital IRB.

PROCEDURE: The following procedure outlines the process for requesting access to stored tissue for research purposes:

1. Investigators must submit their protocol request on an approved form as indicated in the IRB Guidelines.
2. The Principal Investigator will write and submit the protocol to Methodist IRB and is responsible for the protocol, tissue request form (see attached) and the budget.
3. Once the protocol is approved by the IRB, the form requesting access to tissue will be signed/stamped and dated by the IRB Chair. This signed form along with the IRB approval letter will be sent to the Principal Investigator by the IRB Secretary.
4. Investigators requesting access to stored tissue for research purposes must contact Pathology to determine costs associated with tissue preparation.
5. The Principal Investigator will be responsible for faxing the signed tissue request form to Tumor Registry.
6. Tumor Registry will query the database to facilitate a list of names for Pathology Services. Once a list is developed, the signed tissue request form and the patient list will be faxed by Tumor Registry to Pathology Services.
7. Pathology Services will be responsible for preparing the required samples and notifying the Principal Investigator once the samples are ready.
8. Release of tissue is completed per Pathology Services policy.

METHODIST HOSPITAL

An Affiliate of Methodist Health System

Request for Access to Tissue for Research Purposes

Principal Investigator (PI): _____

Contact Phone Number: _____

Study: _____

Date of IRB Submission: _____

Tissue Request

Tumor Type: _____

Number of Samples: _____

Additional Requests: _____

_____

PI Signature / Date: _____

IRB Chair Signature / Date: _____

Instructions:

1. Once signed by both PI and IRB Chair, PI will fax request to Methodist Tumor Registry at 354-3387; Attention: Team Leader (Phone # 402-354-3395)
2. Tumor Registry will then fax this form along with a list of patient names whose tissue meets the above request to Pathology at 402-354-4535; Attention: Laboratory Secretary (Phone # 402-354-4550)
3. Once the specimens are prepared, Pathology will contact the PI
4. Questions about IRB processes or study status should be directed to the Director of Medical Staff Services at 402-354-4036

DOCS/1476520.3