GLOSSARY OF RESEARCH-RELATED TERMS

ASSENT: Agreement by an individual not competent to give legally valid informed consent (e.g., child or mentally limited person) to participate in research.

ASSURANCE: A formal, written statement submitted to a Federal agency that an institution promises to comply with applicable rules governing research with human subjects.

BENEFIT: Something that promotes or protects well being; an advantage.

BIORESEARCH MONITORING PROGRAM: Under this program, the FDA conducts periodic inspections and audits of both clinical investigators and IRBs.

CERTIFICATION: The official notification by the institution to the DHHS that a research project or activity involving human subjects has been reviewed and approved by the IRB in accordance with the approved assurance on file at DHHS. In order for a proposal involving human subjects to be eligible for federal funding, it must first be approved by the IRB and certified by the institutional representative.

CFR (Code of Federal Regulations): A compendium of rules issued by Federal agencies on a multiplicity of topics.

CLASS I, II, III DEVICES: Classification by the Food and Drug Administration of medical devices according to potential risks or hazards.

CLINICAL TRIALS PHASE 1-4: A Clinical trial is a prospective, organized, systematic exposure of subjects to an intervention of some kind (drug, surgical procedure, medical device, etc.) to answer some question about the intervention. The following is a series of terms that pertain to the design of clinical trials:

> **Phase 1 Clinical Drug Trial:** A Phase 1 clinical drug trial represents the first test of a drug in a human population (only animal and *in vitro* data are available). Phase I trials are designed to determine toxicity, absorption, metabo9lism and safe dosage range and are limited to relatively few subjects (20-80). Although healthy volunteers are sometimes used, for obvious ethical reasons, Phase I testing is more properly done in patients. For example, cancer chemotherapy subjects in a Phase I trial have exhausted all alternative treatments and enroll in the study hoping for therapeutic benefit. The study often involves dose escalation until the maximum tolerated dose is established. This means the dose is increased until toxicity occurs. Obviously, subjects in a Phase I clinical trial of a toxic chemotherapeutic agent incur the risk of death from toxicity. Although a subject may receive therapeutic benefit from participating in a Phase I study, the objective in conducting the study is primarily pharmacological in nature.
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> **Phase 2 Clinical Drug Trial:** A Phase 2 clinical drug trial is a controlled clinical trial involving a limited number of subjects (200-300). It is designed to test efficacy and obtain additional data on the safety of the drug.
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> **Phase 3 Clinical Drug Trial:** A Phase 3 clinical drug trial is an expanded trial (several thousand subjects) which is designed to gain additional evidence of efficacy.
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> **Phase 4 Clinical Drug Trial:** A Phase 4 clinical drug trial is a post-marketing study of an FDA-approved drug in order to gain more information, e.g., elucidate the incidence of

a specific adverse reaction or determine the long-term effects of the drug on morbidity and mortality.

Randomized Clinical Trial (RCT): A randomized clinical trial (RCT) is a clinical trial where subjects are randomly assigned (by chance) to different treatments or interventions, such as "Drug A" versus "Drug B."

Single Masked Design: In a single masked design, the subject does not know the treatment assignment but the investigator does.

Double Masked Design: A double masked design is a study comparing two or more treatments where neither the investigator nor the subject knows who has received which treatment. This minimizes potential bias, e.g., assignment of a particular subject to one of the treatments.

Cross-over Design: In a study which employs a cross-over design, subjects are randomly assigned to different treatments and then switched at the halfway point.

Concurrent Control: A concurrent or prospective control is a subject who is not given the treatment or intervention under study and who is compared with subjects given the treatment under study. There are three types of concurrent controls: a concurrent control may be given a placebo (concurrent placebo control) or no treatment (a non-treatment concurrent control), or an active drug (a concurrent active control).

Historical Control: A historical control is a subject for which data are already available (e.g., via medical records). Historical controls are then compared with subjects being treated currently. Historical controls are mainly used in the study of rare diseases where the **n** is not sufficient for a randomized clinical trial. Historical controls are considered to be the least reliable because they compare results obtained in another time, in another place and by another investigator.

Placebo Control: A placebo controlled study is a study where subjects are randomly assigned to a placebo. When there is no established (standard) treatment for a disease, a placebo control is often the design of choice. Indeed, a placebo controlled clinical trial is generally considered to be the most scientifically valid study. However, if a treatment exists that has been shown to be effective, it is unethical to use a placebo, particularly if the illness is life-threatening.

Active Control Study: In an active control study, subjects are randomly assigned to either a recognized effective treatment or the study drug. Active control studies can be difficult to interpret and are generally not considered as scientifically valid as a placebo controlled clinical trial. Differences between treatments can be obscured by such factors as poor compliance, medication errors and poor methods of measurement. These factors are not as significant in a placebo controlled study. However, ethical considerations may not permit use of a placebo. The most common type of drug study that uses an active control is an antibiotic study, because the differences between drugs are easy to distinguish.

Double Masked, Placebo Controlled, Cross Over Design, Randomized clinical Trial: Subjects are randomly assigned to either placebo or study drug. Neither the investigator nor the subject knows the treatment assignment. The treatments are then switched at the halfway point.

Open Label Study: In an open label study subjects are assigned to one treatment only. In an open label study two doses of a drug are often compared.

Retrospective Study: A retrospective study is a study involving data that have already been collected, e.g., a chart review.

The Null Hypothesis: There is widespread agreement that each clinical trial is ethically required to begin with an honest null hypothesis (also called equipoise). That is, the physician investigator must be able to state there is no scientifically valid reason to predict that therapy "A" will be superior to therapy "B" (and there is no further alternative "C" which is known to be better than A and B). Thus, a physician investigator can honestly tell a prospective subject that whether they are randomly assigned to A or B they will be receiving the best available treatment.

In reality, there is usually some preliminary data to suggest one therapy may be better than the other. However, in terms of scientific validation, investigators often state the existence of a null hypothesis based upon the requirement to achieve statistical significance. Scientific validation requires a standard of significance at the P 0.05 level, i.e., the results are 95% certain, meaning that the possibility of the differences between treatments resulting from chance is 5 in 100. Both the FDA and the pharmaceutical industry have accepted this standard.

COMPENSATION: Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research.

COMPETENCE: Technically, a legal term, used to denote capacity to act in one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice.

CONFIDENTIALITY: Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others in ways that are inconsistent with the understanding of the original disclosure without permission.

DEBRIEFING: Giving subjects previously undisclosed information about the research project following completion of their participation in research.

EMBRYO: Early stages of a developing organism, broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (i.e., from conception to the eighth week of pregnancy).

EQUITABLE: Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed.

ETHICAL CODES AND STATEMENTS OF ETHICAL PRINCIPLES: There are three major ethical codes that provide general ethical guidelines for the responsible conduct of research in the United States and which provide the basis for the HHS/FDA regulations on the protection of human research subjects. It should be noted that HHS/FDA regulations are not intended to serve as an ethical code. In fact, 45 CFR 46.103 requires each institution's Assurance of Compliance to include a statement of principles for ethical conduct of research which may be based upon "an appropriate existing code, declaration or statement of ethical principles." Most institutions use the Belmont Report, Declaration of Helsinki and the Nuremberg Code.

Nuremberg Code: An international ethical code published in 1947 which established standards for the conduct of research involving human beings. It arose out of the Nuremberg War Crimes Trial, where 23 Nazis were charged with crimes against humanity that involved murderous pseudomedical experimentation. Twenty of the individuals charged were physicians.

Declaration of Helsinki: An international ethical code first issued in 1964 by the 18th World Medical Assembly in Helsinki, Finland. The Declaration contains 12 basic principles which are similar to the Nuremberg Code but represent an expansion of what constitutes acceptable research and the ethical responsibilities of investigators. Unlike the Nuremberg Code, the Declaration of Helsinki addresses the need for peer review (i.e., IRB review). It is interesting to note that the FDA will not accept foreign data unless the studies in which such data are generated are conducted in compliance with the Declaration of Helsinki (21 CFR 312.20, 46 Fed Reg 8953, Tuesday, January 17, 1981).

Belmont Report: A report consisting of ethical principles and guidelines for protection of human subjects in research. It was issued April 18, 1979, by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

EXPEDITED REVIEW: Review of proposed research by a designated reviewer rather than by the entire IRB. Federal rules permit expedited review for certain types of low risk research.

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

FDA: Food and Drug Administration, an agency of the Federal government, established by Congress in 1912 and presently part of the Department of Health and Human Services (HHS). FDA regulations apply only to research involving FDA-regulated products. HHS regulations, however, apply to all human subject research conducted at the University of Rochester.

FETUS: The developing human organism from the time of implantation until delivery; generally refers to later phases of development.

HHS: A Federal agency: U.S. Department of Health and Human Services; formerly HEW. The HHS regulations apply to all human subject research conducted at the University of Rochester.

HUMAN SUBJECT: A living individual about whom an investigator (whether professional or study) conducting research obtains: 1) data through intervention or interaction with the individual, or 2) identifiable private information. "Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulation of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). **NOTE:** FDA defines "human subject" as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

INCAPACITY: When referring to a person's mental status, incapacity means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

INCOMPETENCE: Technically, a legal term meaning inability to manage one's own affairs. Often used as a synonym for incapacity.

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

INSTITUTION: Any public or private entity or agency (including federal, state or other agencies).

INSTITUTIONALIZED (mentally disabled): Confined, either voluntarily or involuntarily, in a facility for the care of the mentally or otherwise disabled (e.g., a psychiatric hospital, home or school for the retarded).

INVESTIGATIONAL DRUG: Includes those substances in any of the clinical stages of evaluation which have not been released by the FDA for general use or cleared for sale in interstate commerce. An investigational drug may also be defined by one of the following:

a. A drug in any of the clinical stages of evaluation (Phase I, II, III) which has not been released by the FDA for general use or cleared for sale in interstate commerce.
b. Any commercially available drug proposed for a new use.
c. A new dosage form or method of administration.
d. A commercially available drug which contains a new component such as an excipient, coating or menstruum.
e. A new combination of two or more commercially available drugs.
f. A combination of commercially available drugs in new proportions.

Investigational New Drug – Exemption (IND): An IND (Form FDA 1571) is an application filed (usually by the sponsor) with the FDA that includes a detailed description of the planned investigation including Phase I, II and III studies. The application must also contain names and addresses of the investigators and identification of the IRB responsible for initial and continuing review and approval of the proposed study. The FDA has 30 days to review the IND and notify the sponsor if approval is withheld. The applicable FDA regulation for INDs is 21 CFR 312.1. Each investigator who will participate in the study must provide the sponsor with a completed Statement of Investigator (Form FDA 1572) as required by 21 CFR 312.53(c). This form addresses investigator training and experience as well as investigator commitments.

Investigational New Drug (Treatment IND): A treatment IND is a procedure under which a new investigational drug can be made available to patients with life-threatening or serious diseases outside a clinical trial. Under the treatment IND regulations [21 CFR 312.34] an investigational drug which is currently the subject of a clinical trial (usually Phase II or III) under an IND can be given to desperately ill patients via a treatment IND.

Investigational New Drug – Compassionate Use: If a physician wishes to use a non-FDA approved drug which does not have an IND (e.g., drug investigated or marketed abroad), a treatment IND cannot be issued. However, compassionate use approval can be issued by the FDA.

Investigational New Drug Application: Once the clinical evaluation of a drug is completed, an NDA must be submitted to FDA to obtain approval to market the drug. The NDA regulations are 21 CFR 314. In an NDA review there is a much closer scrutiny of the data by FDA to ensure safety and efficacy. In contrast, the IND review requires only enough evidence of effectiveness to justify a clinical trial.

INVESTIGATIONAL MEDICAL DEVICE: A medical device is defined as any health care product that does not achieve any of its intended purposes by chemical action or by being metabolized. Before 1976, medical devices could be marketed without review by the FDA.

However, in 1976 the medical device amendments of 1976 to the Federal Food, Drug and Cosmetic Act were passes in order to ensure that new devices were safe and effective before they were marketed. The FDA regulations which govern medical devices are 21 CFR 812, 814, 860, 861. An investigational medical device is a device not yet approved for marketing by the FDA.

INVESTIGATIONAL DEVICE EXEMPTION (IDE): An IDE is like an IND for a new drug. It allows an unapproved medical device to be used for investigational purposes. FDA has 30 days to review the IDE and notify the sponsor if approval is withheld. The requirements for an IDE are similar to an IND and are designed to ensure that the sponsor conducts adequate preclinical testing, selects appropriate subjects for clinical research, obtains IRB approval, obtains adequate informed consent, uses qualified investigators, monitors the investigation, and collects data promptly. In deciding whether to approve an IDE, the FDA focuses on how the investigation will be conducted rather than on a precise risk-benefit analysis. The IDE regulation is 21 CFR 812 (45 Fed Reg 3751, January 19, 1980).

Medical devices are classified as non-significant risk (NSR) and significant risk (SR) by the sponsor and the IRB. If a sponsor designates a device as NSR and the IRB agrees, the investigation may begin without submission of an IDE (under the abbreviated IDE requirements). If, however, the IRB determines the device is SR, an IDE must be submitted before the study can be initiated. In this circumstance, it does not matter if the sponsor has classified the device as SR or not because the IRB has ultimate responsibility.

IN VITRO: Literally, "in glass" or "test tube" – used to refer to processes that are carried out outside the living body, usually in the laboratory, as distinguished from *in vivo*.

IN VIVO: In the living body; processes, such as the absorption of a drug by the human body, carried out in the living body rather than in a laboratory.

LEGALLY AUTHORIZED REPRESENTATIVE: A person authorized either by statute or by court appointment to make decisions on behalf of another person. In the research context a legally authorized representative is an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

MATURE MINOR: Someone who has not reached adulthood (as defined by state law), but who may be treated as an adult for certain purposes (e.g., consenting to certain types of medical care).

MENTALLY DISABLED: Having either a psychiatric disorder (e.g., psychosis, neurosis, personality, or behavior disorder), a developmental disorder (e.g., mental retardation), or a neurological disorder that affects cognitive or emotional functions to the extent that capacity for judgment is significantly diminished.

MINIMAL RISK: Minimal risk means "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." Examples of research activities involving no more than minimal risk include collection of blood samples from healthy, non-pregnant adults by venipuncture in amounts not exceeding 450 ml in an eight-week period and no more often than two times per week; electrocardiography; electroencephalography; and moderate exercise by healthy subjects.

MINOR: A person who has not attained the legal age for consent to treatment or procedures involved in research under the applicable law of the jurisdiction in which the research will be conducted (18 years in the state of New York).

NATIONAL COMMISSION: In July 1974, in response to widespread publicity concerning unethical human experimentation in the U.S. (e.g., Tuskegee Syphilis Study, Jewish Chronic Diseases Hospital Study, Willowbrook Study, San Antonio Contraceptive Study), Congress passed the National Research Act (Public Law 93-348), which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The charge of the Commission was to conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects. Although both FDA and HHS had regulations for the protection of human subjects, they were obviously inadequate in light of the many human subject abuses that occurred in medical and behavioral research conducted in the U.S.

From 1975 through 1978 the Commission published eight reports on various aspects of research involving human beings. These reports formed the basis for the development of the 1981 DHHS and FDA regulations. Undoubtedly, the most ethically fundamental report produced by the Commission was the Belmont Report. The other reports produced by the National Commission are: Research on the Fetus (1975), Research Involving Prisoners (1976), Research Involving Children (1977), Research Involving Those Institutionalized as Mentally Infirm (1978), Institutional Review Boards (1978), Ethical Guidelines for the Delivery of Health Services by DHEW (1978). The National Commission disbanded in 1978.

OPRR: Office for the Protection from Research Risks at NIH, responsible for implementing HHS regulations governing research with human subjects.

PREGNANCY: Encompasses the time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

PRESIDENT'S COMMISSION: The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research succeeded the National Commission. The President's Commission had a broader mandate to study ethical issues, and it published during 1981-1983 a series of ten reports dealing with various aspects of medical ethics and human subjects research. The President's Commission wrote on topics such as genetic engineering, access to health care, genetic screening and counseling, whistle-blowing, and the adequacy of the Federal regulations.

PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH: An interdisciplinary advisory group, established by Congressional legislation in 1978, that issued reports on ethical problems in health care and in research with human subjects.

PRINCIPAL INVESTIGATOR: The scientist or scholar with primary responsibility for the deign and conduct of a research project.

PRIVACY: Control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

PROTOCOL: The formal design or plan of an experiment or research activity; specifically, the plan submitted to an IRB for review and to an agency for research support.

RESEARCH: A systematic investigation designed to develop or contribute to generalizable knowledge. The following are a series of relevant terms:

THERAPY: "Therapy" refers to interventions that are applied solely to enhance the well-being of an individual patient who is sick. The interventions are procedures commonly accepted by the medical community and represent the standard of care.

INNOVATIVE THERAPY: Innovative therapy represents a deviation from standard medical practice. Physicians are free to innovate if the innovative procedure is applied solely to enhance the well-being of their patient. However, when innovative therapy differs significantly from routine practice it should be viewed and treated as experimental, with appropriate safeguards in place to protect the rights and welfare of the patients (subjects) (e.g., RSRB review, informed consent, etc.). In order to validate innovative therapy, the innovative procedure should be subjected early on to an evaluation via a formal research protocol.

THERAPEUTIC RESEARCH: "Therapeutic research" refers to interventions that are designed to determine the efficacy and safety of a therapeutic or diagnostic method. The interventions are not applied solely to enhance the well-being of the individual subject who is sick (note use of the term "subject" as opposed to "patient"). Achievement of maximum possible therapeutic benefit cannot, therefore, be presumed, since the intervention is still being evaluated. The objective of therapeutic research is to increase generalized knowledge (i.e., test a hypothesis and draw conclusion), and at the same time provide the subject with a needed health benefit. Accordingly, the responsibilities of a physician who is also an investigator must take into consideration the fact that the patient is also a research subject.

NON-THERAPEUTIC RESEARCH: Research that has no likelihood of intent of producing a diagnostic, preventive, or therapeutic benefit to the current subjects, although it may benefit subjects with a similar condition in the future.

RISK: A potential harm that a reasonable person, in what the investigator knows or should know to be the subject's position, would be likely to consider significant in deciding whether or not to participate in the research.

TEST ARTICLE: A general term that encompasses drugs, devices, food additives, etc. that are regulated by the FDA.

VIABLE: As it pertains to the fetus, means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. Once a fetus is viable it is a premature infant.

VOLUNTARY: Free of coercion, duress or undue inducement; used in research context to refer to a subject's decision to participate (or to continue to participate) in a research activity.