

## **Appendix A**

### **DEFINITIONS AND TERMS**

**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 likely to interfere with the results in a placebo-controlled study. However, ethical considerations may not permit use of a placebo.

**ADVERSE EVENT:** Any untoward occurrence in a research participant. The occurrence need not have a clear causal relationship with the individual's participation in the research; an AE can be any unfavorable and unintended sign, symptom, event or occurrence affecting a participant's physical, mental, social, financial, legal, or psychological well-being. An unanticipated AE should be reported to the committee as soon as possible after it is identified.

**ALLEGATION OF NONCOMPLIANCE:** An unproven assertion of noncompliance.

**AMENDMENT:** The term amendment includes any changes to previously approved research.

Investigators may not initiate any changes in research procedures or consent form(s) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subject (Note: IRB Approval of the actions taken in this circumstance must still be sought after the fact). Examples of amendments that require IRB review include, but are not limited to, changes in:

- Study personnel;
- Advertising materials (flyers, radio spots, etc.);
- Research procedures;
- Subject populations (e.g., inclusion or exclusion criteria);
- Location where research will be conducted;
- Consent form (including translations);
- Recruitment procedures;
- Study design or methods.

**ASSENT:** Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research. An assent is typically paired with permission from a parent or guardian, and together they comprise the informed consent to participate.

**ASSURANCE:** A formal written, binding commitment that is submitted to a federal agency in which an institution agrees to comply with applicable regulations governing research with human subjects and stipulates the procedures through which compliance will be achieved. NYCC's Assurance number is FWA00001657.

**ATTEND:** When the term is used in reference to attending an IRB meeting the term is meant to encompass both physical attendance and attendance via teleconference so long as all members are connected simultaneously.

**AUTHORIZED INSTITUTIONAL OFFICIAL:** An officer of an institution with the authority to speak for and legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human subjects in biomedical and behavioral research.

**BELMONT REPORT:** A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978. A summary of the Belmont Report is available at <http://www.fda.gov/oc/ohrt/IRBS/belmont.html> These principles permeate human subjects research to this day.

**BENEFICENCE:** An ethical principle discussed in the [Belmont Report](#) that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

**BENEFIT:** A valued or desired outcome; an advantage. UNLV's human research application requests information about the direct benefits accruing to the research participants.

**CFR (Code of Federal Regulations):** The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation. Each volume of the CFR is updated once each calendar year and is issued on a quarterly basis. Each title is divided into chapters, which usually bear the name of the issuing agency. Each chapter is further subdivided into parts that cover specific regulatory areas. Large parts may be subdivided into subparts. All parts are organized in sections, and most citations in the CFR are provided at the section level.

**CHILDREN:** Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.401(a)]. In Nevada, individuals younger than 18 years of age are

considered children for most research situations, and informed consent then consists of the child's assent and the parent's permission. (See also: Assent)

**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:

- Active Control Study
- Concurrent Control
- Cross-over Design
- Double Blinded Design
- Double Blinded, Placebo Controlled, Cross-Over Design, Randomized Clinical Trial
- Historical Control
- Open-Label Study
- PHASE 1; PHASE 2; PHASE 3; PHASE 4
- Placebo-Controlled
- Randomized Controlled Design
- Retrospective Study
- Single Blinded Design
- The Null Hypothesis

**COERCION** This occurs when an overt threat of harm is intentionally presented by one person in order to obtain compliance (Belmont Report). To be coercive, a subject who refuses must be made worse off than if he or she would have been, if never asked even if the harm is only perceived. Coercion occurs, for example, in cases where retribution is conceivable or perceived by the subject. Examples of coercion include situations where it is implied that continued services are dependent upon participation in the research; or where refusal may affect some future care or outcome. Inducements (including payment) are not considered coercion for the purposes of NYCC's IRB. See Undue Influence concerning when judgment may be compromised by financial incentives especially when the subject is not the recipient of the financial incentive. The IRB must eliminate all sources of coercion.

**COGNITIVELY IMPAIRED:** Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling

physical handicaps, may also be compromised in their ability to make decisions in their best interests.

**COMPENSATION:** Payment for participation in research. Compensation should be appropriate for the amount of effort involved, and not excessive and thereby coercive. Compensation is not considered a benefit.

**COMPETENCE:** Technically, a legal term, used to denote capacity to act on 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. (See also: Incompetence, Incapacity)

**CONCURRENT CONTROL:** A concurrent or prospective control is a subject who is not given the treatment or intervention under the study and who is compared with subjects given the treatment under the 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).

**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 without permission in ways that are inconsistent with the understanding of the original disclosure.

**CONSENT:** *See Informed Consent*

**CONTINUING NONCOMPLIANCE:** A pattern of recurring (in one or more protocols simultaneously or over a period of time) or ongoing instances of actions or omissions (noncompliance) which indicate: 1) an underlying deficiency in knowledge of the regulations and IRB requirements or; 2) a possible inability or unwillingness to comply with them. Instances may or may not constitute serious noncompliance.

- Continuing noncompliance is defined as a series of more than one noncompliance event, in reasonably close proximity, that indicates the need for evaluation of the methods and systems used to protect human subjects. Continuous noncompliance need not involve a sequence of similar events if the events, taken as a whole, indicate that examination of the methods and systems used is warranted.

**CONTINUING REVIEW OF RESEARCH (OR CONTINUING REVIEW):** The term “continuing review” designates the review of requests to re-approve a study for continuation at any time after initial approval is granted.

**CONTROL (SUBJECTS) or CONTROLS:** Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of study. Control conditions may be

concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment, the study is considered historically controlled.

**CONTROLLED STUDY:** Before a new drug or biologic can be marketed, its sponsor must show, through adequate and well-controlled clinical studies, that it is effective. A well-controlled study permits a comparison of subjects treated with the new agent with a suitable control population, so that the effect of the new agent can be determined and distinguished from other influences, such as spontaneous change, "placebo" effects, concomitant therapy, or observer expectations. FDA regulation 21 CFR 314.126 cites five different kinds of controls that can be useful in particular circumstances:

- (1) placebo concurrent control
- (2) dose-comparison concurrent control
- (3) no-treatment concurrent control
- (4) active-treatment concurrent control, and
- (5) historical control

No general preference is expressed by the FDA for any one type, but the study design chosen must be adequate to the task.

**CO-PRINCIPAL INVESTIGATOR (CO-PI):** The other primary scholar or researcher involved in conducting the research; if the project is for a thesis or dissertation, the student is the co-PI.

**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.

**DATA and SAFETY MONITORING BOARD (DSMB):** A Data and Safety Monitoring Board is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the IRB and sponsors for stopping the trial for efficacy, for harms, or for futility. Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and ensure patient safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring entity or be available if warranted.

**DATA SAFETY MONITORING PLAN (DSMP):** At minimum, all investigators must provide a "plan" for ensuring data integrity and safety monitoring for human subjects who are involved in the research. The level of detail in the plan should be based on the degree of risk to research subjects. The IRB will consider the investigator's plan for collection, monitoring, storage, and

analysis of data. The level of monitoring required is related to the degree of risk posed by the research.

**DEBRIEFING:** Giving subjects previously undisclosed information about the research project following completion of their participation in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtaining rather than imparting information.)

**DECEPTION:** Deception is the intentional misleading of subjects or the withholding of full information about the nature of the experiment. Misleading or omitted information might include the purpose of the research, the role of the researcher, or what procedures in the study are actually experimental. Deception increases ethical concerns, because it interferes with the ability of the subject to give informed consent. However, deception is arguably necessary for certain types of behavioral research. Because humans act differently depending on circumstances, full knowledge by the subject might bias the results.

### ***Regulations***

- Federal regulations permit but establish limitations on the use of deception. The Investigator must provide scientific and ethical justification for deceptive procedures for the IRB review and approval. The missing information should not increase the risks of the study, and subjects must be fully debriefed. Subjects must have the opportunity to ask questions about the new information and be given the opportunity to withdraw from the study and have their data removed. Deception may not be utilized to obtain enrollments.
- Some research can only be conducted without the full knowledge of the research subjects. Yet the use of deception in research raises special problems that the IRB will review closely. One consideration is whether the deception is necessary. Present federal rules prohibit the use of deceptive techniques which place subjects at more than minimal risk.
- IRBs expect investigators to ***debrief*** subjects who have been deceived during participation in research activities. The debriefing should include a detailed description of the ways in which deception was used. The investigator is responsible for ensuring that the subject leaves the research setting with an accurate understanding of the deception. The debriefing process, including any written materials, should be explained to the IRB as a part of submitted protocols.

**DECLARATION OF HELSINKI:** A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975 and 1989.

**DESCRIPTIVE STUDY:** Any study that is not truly experimental (e.g., quasi-experimental studies, correlational studies, record reviews, case histories, and observational studies).

**DEVIATION:** Changes in the conduct of the IRB-approved study plan (e.g., protocol) without the IRB's prior approval. Deviations can be: 1) minor or administrative protocol deviations; 2) emergency deviations; or 3) major, non-emergent deviations.

Minor or administrative protocol deviations are those which do not affect the scientific soundness of the research or adversely affect the rights, safety, or welfare of human subjects. A minor or administrative protocol deviation is limited to minor departures from the protocol for a single subject. Examples include: follow-up visits that occurred outside the protocol-required timeline or blood samples obtained at times close to but not precisely at the time points specified in the protocol. Events limited to minor or administrative deviations do not constitute non-compliance and are summarized to the IRB during continuing review.

Emergency deviations occur in an emergency situation, such as when a departure from the protocol is required to eliminate apparent immediate hazard to the subject. Examples include: withholding study drug in response to a serious adverse event (actual harm) or to avoid a serious harm (risk of harm). Emergency deviations are considered Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and are reported to the IRB using the appropriate UPIRSO reporting form.

Major, non-emergent deviations are any planned changes in the IRB-approved study plan that are not a minor/administrative protocol deviation or an emergency deviation. Major, non-emergent deviations may not be initiated without prior IRB review and approval. Examples include: any changes to the study design or procedures or changes to study staff or sites). To obtain IRB approval, the modification to the study plan must be submitted using the amendment request form. Major, non-emergent deviations that are implemented before IRB approval are considered a failure to conduct the study as directed by the IRB (noncompliance) and must be promptly reported to the IRB using the noncompliance report form.

Deviations and Exceptions are both considered violations. Deviations however, occur prior to IRB approval and exceptions are violations to the protocol that are instituted after IRB approval for them is granted (through the amendment system, though not truly amending the protocol so much as advising the IRB that for one subject or for some specific reason the protocol will not be followed but immediately thereafter the protocol will continue as previously approved).

**DEVICE (See also Medical Device):** A device per the FDA is: "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: 1) recognized in the United States Pharmacopeia–National Formulary (USP–NF <http://www.usp.org/USPNF/>), or any supplement to them, 2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or 3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

**DHHS:** The Department of Health and Human Services, under the Secretary of Health and Human Services, is responsible for “Improving the health and well-being of America”. The National Institutes of Health (NIH), Center for Disease Control (CDC), Health Resources and Services Administration (HRSA) and the Substance Abuse and Mental Health Services Administration are examples of DHHS agencies. Also abbreviated as HHS.

**DIETARY SUPPLEMENT:** Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994. A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The "dietary ingredients" in these products may include: vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet. Whatever their form may be, DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement. If a research study is intended to show a certain health benefit, the supplement may be subject to regulation as a drug in that the study is considered to be designed to make a drug claim.

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), the dietary supplement manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed. FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market as well as reviewing safety information in 75-day premarket notifications for new dietary ingredients, to ensure that such products are reasonably expected to be safe (21 CFR 190.6). As of August 24, 2007, manufacturers of dietary supplements are required to follow current good manufacturing practices (cGMPs) for dietary supplements, known as the final cGMP rule.

**DISSENT:** Behaviors that would indicate an individual does not want to participate (Where seeking assent, dissent behaviors may be interpreted in certain studies as simply moving away, certain facial expressions, head movements, etc.)

**DOUBLE BLINDED, 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.

**DOUBLE BLINDED DESIGN:** A double blinded 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.

**DRUG:** A drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

**DRUG CLAIM:** A drug claim is that the product is useful in diagnosing, mitigating, treating or curing a specific disease or class of diseases. Nutrient content claims characterize the level of a nutrient in a food (e.g., "high in fiber"). Health claims describe the role of a food substance in reducing the risk of a disease (e.g., "Adequate folate in healthful diets may reduce a woman's risk of having a child with a brain or spinal cord birth defect. "). If a research study is intended to show a certain health benefit, care should be taken to consider whether the research is intended to claim that a dietary supplement is useful in diagnosing, mitigating, treating or curing a specific disease or class of diseases, as these are drug claims, not health claims. Dietary supplements that bear such disease claims are subject to regulation as drugs.

**EMANCIPATED MINOR:** A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation. (See also: (Mature Minor)

**EMERGENCY DEVIATIONS:** Occur in an emergency situation, such as when a departure from the protocol is required to eliminate apparent immediate hazard to the subject. Examples include: withholding study drug in response to a serious adverse event (actual harm) or to avoid a serious harm (risk of harm). Emergency deviations are considered Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) and are reported to the IRB using the appropriate UPIRSO reporting form.

**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.

**EXCEPTION:** Exceptions are violations to the protocol that are instituted after IRB approval for them is granted (through the amendment system, though not truly amending the protocol so much as advising the IRB that for one subject or for some specific reason the protocol will not be followed but immediately thereafter the protocol will continue as previously approved).

**EXISTING DATA:** Existing data exists at the time of the submission. Data that exists when the investigator goes to the record to look for it is not necessarily existing data if it was not already in existence before the study was submitted. This distinction prevents any ethical issues from arising from the review of data for which the investigator may have had influence over without the added protections that come from the review of non-exempt human subjects research.

**EXPEDITED REVIEW:** Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

**EXTERNAL ADVERSE EVENT:** From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

**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).

**FEDERAL POLICY (THE):** The federal policy that provides regulations for the involvement of human subjects in research. The Policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the Policy applicable to such research. Currently, sixteen federal agencies have adopted the Federal Policy. (Also known as the "Common Rule.")

**FEDERALWIDE ASSURANCE (FWA):** The Federalwide Assurance (FWA) is the only type of new assurance of compliance accepted and approved by OHRP for institutions engaged in non-exempt human subjects research conducted or supported by HHS. Under an FWA, an institution commits to HHS that it will comply with the requirements set forth in 45 CFR part 46, as well as the Terms of Assurance.

**FETUS:** The product of conception, from the time of implantation until delivery.

**FINAL RULE cGMPs FOR DIETARY SUPPLEMENTS:** The U.S. Food and Drug Administration issued the final rule establishing regulations to require current good manufacturing practices (CGMPs) for dietary supplements. The final CGMP is effective August 24, 2007. To limit any disruption for dietary supplements produced by small businesses, the rule has a three-year phase-in for small businesses. Companies with more than 500 employees have until June 2008 to comply, companies with less than 500 employees have until June 2009 to comply, and companies with fewer than 20 employees have until June 2010 to comply with the regulations. If a research study is intended to show a certain health benefit the a dietary supplement may be subject to regulation as a drug in that the study is considered to be designed to make a drug claim.

**FINDING OF NONCOMPLIANCE:** Noncompliance that is supported by a preponderance of evidence. A finding of noncompliance may exist because there is clear evidence, an admission supported by evidence, or an investigation into an allegation has determined the allegation to be supported by a preponderance of evidence.

**FULL BOARD REVIEW:** Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting.

**GUARDIAN:** An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care.

**HALT TO RESEARCH:** Is a cessation of some or all research activities voluntarily initiated by the Principal Investigator or sponsor (for example temporarily stopping enrollment or other research procedures, placing the study “on hold”). This does not constitute IRB suspension or termination.

**HEALTH INFORMATION:** Any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual. This constitutes a larger set of information which may be broken down into that health information which is not identifiable and that which is **identifiable health information**

**HELSINKI DECLARATION:** See: Declaration of Helsinki

**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 by investigators because they compare results obtained in another time, in another place and by another investigator.

**HUMAN SUBJECTS:** Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations, human subjects are defined as living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information.

**IDENTIFIABLE:** Identifies the individual; or with respect to which there is a reasonable basis to believe the information can be used to identify the individual. Not all identifiable information is necessarily identifiable health information. This would only be the case if it was actually associated with health information.

**INCAPACITY:** Refers to a person’s mental status and 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:** A legal term meaning inability to manage one’s own affairs, and often used as a synonym for incapacity.

**INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:** Information that is a subset of health information, including demographic information

collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

**INDIVIDUALLY IDENTIFIABLE PRIVATE INFORMATION:** Private information or specimens are individually identifiable when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Private information or specimens are not individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, if the following conditions are both met:

(1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

(2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

(a) the key to decipher the code is destroyed before the research begins;

(b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement);

(c) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or

(d) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

**INDUCEMENTS (POTENTIAL FOR UNDUE INFLUENCE):** Inducements are offers that get people to do things they may not otherwise do. Inducements or incentives, rewards or payments may be acceptable depending on the population, level and type but they may also be considered undue influence if the reward/payment is so large as to persuade the person to take undue risks or volunteer against their better judgment. Another concern about undue influence (unacceptable inducements) is they can result in a subject lying or concealing information that may otherwise exclude them from the research. As a result, if the study involves no risk or minimal risk, the concern over undue influence is

reduced. The IRB should consider ways to reduce the influence of payments or rewards that undermine a person's capacity to exercise free choice and could invalidate consent. The IRB should balance the need to reduce undue influence with the need to avoid exploitation of populations.

**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. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the investigator, the sponsor, the institution or agents thereof from liability for negligence.

**INITIAL REVIEW OF RESEARCH:** or initial review. The term initial review designates the review of new, not previously approved research including new studies tabled/deferred at previous meetings.

**INSTITUTIONAL REVIEW BOARD (IRB):** A specially constituted, federally mandated review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. UNLV has two IRB's – Social Behavioral and Biomedical.

**INTERNAL ADVERSE EVENT:** From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

**INVESTIGATOR:** A researcher conducting the project. Investigators can be principal investigators or co-principal investigators. Students are always co-principal investigators.

**IRB:** See: **Institutional Review Board**

**JUSTICE:** An ethical principle discussed in the Belmont Report requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances or characteristics similarly.

**KEY PERSONNEL:** Term used to indicate any individual responsible for the design, conduct, and reporting of research for a given study. Key personnel may or may not include the following: study staff, investigators, individuals engaged in human research and individuals not engaged in human research.

**LEGALLY AUTHORIZED REPRESENTATIVE:** A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, 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 medical care). Note that a mature minor is not necessarily an emancipated minor. (See also: Emancipated Minor).

**MAJOR CHANGE (TO PREVIOUSLY APPROVED RESEARCH):** A major change is any modification that is not minor. A major change fundamentally alters any required element of informed consent or fundamentally alters any of the criteria for IRB approval under 45CFR 46.111. (See also substantive).

**MINIMAL RISK:** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed 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. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

**MINIMIZING RISK:** Federal regulations describe minimizing risks to subjects (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes. Therefore using the least number of procedures possible to answer the research question is a method of minimizing risk when additional procedures are required. Addressing whether you have minimized risk requires addressing all three aspects of this definition.

**MINOR:** A person who has not attained the legal age of majority under the applicable law of the jurisdiction in which the research will be conducted (18 years), and therefore as a general rule cannot consent to treatment or procedures involved in research.

**MINOR CHANGE (TO PREVIOUSLY APPROVED RESEARCH):** Minor Changes are those changes that do not significantly alter the prior determinations of the IRB required for approval of research under HHS regulations at 45 CFR 46.111 (in particular, the determinations under 45 CFR 46.111(a)(1) and (2)). However, changes to previously approved research are only minor changes if the IRB chairperson (or another experienced IRB member designated to conduct expedited review by the chairperson) determines those changes to be minor and therefore eligible for expedited review.

For expedited research, a minor change is a modification that does not change the study's eligibility for expedited review.

The following is an example based on OHRP's posting of its September 29, 2008 memorandum. That memorandum was posted in the belief that others may find useful OHRP's clarifications regarding several issues related to the implementation of changes to protocols and informed consent documents. If new or modified risk information is submitted with the sponsor's( or the investigator's) assessment indicating the new or modified risk information does not adversely impact the overall risk-benefit relationship for the subjects of the research and the IRB Chairperson or designated reviewer concurs and documents that those changes do not significantly alter the prior determinations of the IRBs required for approval of research under HHS regulations at 45 CFR 46.111 (in particular, the determinations under 45 CFR 46.111(a)(1) and (2)) the changes are minor and therefore eligible for expedited review.

**MINOR NONCOMPLIANCE:** is a noncompliant event that does not impact the subject safety, compromise the integrity of study/data, violate a subject's rights or welfare or affect the subjects willingness to participate in the research. Minor noncompliance may be reported through the policies governing exemptions and deviations or by contacting the Research Department if there are questions as to how it should be reported.

**MINOR OR ADMINISTRATIVE PROTOCOL DEVIATIONS:** are departures from the approved study plan which do not affect the scientific soundness of the research or adversely affect the rights, safety, or welfare of human subjects. A minor or administrative protocol deviation is limited to minor departures from the protocol for a single subject. [Examples include: follow up visits that occurred outside the protocol required timeline or blood samples obtained at times close to but not precisely at the time points specified in the protocol]. Events limited to minor or administrative deviations do not constitute non-compliance and are summarized to the IRB during continuing review.

**MODIFICATION OF RESEARCH:** (Also see amendments). The term modifications includes any changes to previously approved research. Investigators may not initiate any changes in research procedures or consent form(s) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subject. Examples of modifications that require IRB review include, but are not limited to, changes in:

- Study personnel;
- Advertising materials (flyers, radio spots, etc.);
- Research procedures;
- Subject populations (e.g., inclusion or exclusion criteria);
- Location where research will be conducted;
- Consent form (including translations);

- Recruitment procedures;
- Study design or methods.

**MOU:** Memorandum of Understanding

**MULTICENTER RESEARCH:** Research conducted at more than one location and under the jurisdiction of more than one IRB.

**MULTI-SITE RESEARCH:** Research conducted at more than one location and under the jurisdiction of only one IRB.

**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.

*Note: Before its education functions were split off in 1979, DHHS was called the Department of Health, Education, and Welfare (DHEW)*

**NEONATES:** Newborns are only considered neonates until they are determined to be viable. Once they are determined to be viable, they are considered children.

**NONAFFILIATED MEMBER:** A federally mandated member of an Institutional Review Board who has no ties to the parent institution, its staff, or faculty. This individual is usually from the local community (e.g., business person, attorney, teacher,).

**NONCOMPLIANCE:** Conducting research in a manner that disregards or violates federal regulations, failure to follow the requirements and determinations of the IRB, or institutional policies and procedures applicable to human research, which can be characterized by severity of the event and the pattern of like or similar events. Noncompliance with IRB and/or federal requirements may involve a range of issues from relatively minor or technical violations which result from inadvertent errors, inattention to detail, or inadequate training and supervision of research staff to more [serious noncompliance](#) violations, which pose risk to subjects or others and/or violations of their rights and welfare. Noncompliance does not include minor or administrative protocol deviations that are defined as those which do not affect the scientific soundness of the research or adversely affect the rights, safety, or welfare of human subjects. A minor or administrative protocol deviation is limited to minor departures from the protocol for a single subject.

- Noncompliance is defined as any violation of any regulation that governs human subject research, any deviation from the study protocol approved by the IRB; or any violation of any conditions imposed by the IRB on the approved study or conduct of the research.

**NO-TREATMENT CONTROL:** Placebo Control, No-Treatment Control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control. The alternative study design generally proposed to these kinds of studies is an active-treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent. There are circumstances in which this is a fully valid design.

**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.

**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.

**NUREMBERG CODE:** A code of research ethics developed during the trials of Nazi war criminals following World War II and widely adopted as a standard during the 1950s and 1960s for protecting human subjects.

**NUTRITIONAL SUPPLEMENT:** See Dietary Supplement.

**OFF-SITE RESEARCH:** Designates research conducted at study sites that are not part of NYCC. Off-site locations require review by NYCC IRB if key personnel on the project are performing research activities associated with their NYCC affiliation at the off-site location. Approval of the research is conducted by IRB responsible for the off-site location.

**OFFICE OF HUMAN RESEARCH PROTECTION (OHRP):** The office within the Department of Health and Human Services, responsible for implementing DHHS regulations (45CFR46 Part 46) governing research involving human subjects.

**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.

**PERMISSION:** The agreement of parent(s) or guardian to the participation of their child or ward in research.

**PLACEBO-CONTROLLED:** 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. Although a placebo controlled clinical trial is generally considered to be the most scientifically valid study other scientifically valid study designs like Active Control and Historical Control are among the [five different kinds of controls](#) equally acceptable by the FDA in support of a drug claim when placebo control is ethically questionable. However, if a treatment exists that has been shown to be effective, it is generally considered unethical to use a placebo without strong justification, particularly if the illness is life-threatening. Investigators should indicate, in their request to use placebo, whether it is their opinion that “Standard care is generally considered to be effective and not routinely refused because of the toxicity.” [If applicable they should in addition indicate whether it is their opinion of the investigator that:] “The rationale for the use of placebo instead of effective standard therapy includes that it is not expected to cause irreversible health problems or extreme suffering.” [Use of placebo in this manner would not likely be approved by the IRB without strong justification.] [Use of placebo would also require a thorough description of the risk of being placed on placebo (risk of not receiving standard care) in the risk section]

It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early "escape" mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. In some cases randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are randomly assigned to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint.

IRBs may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials, regardless of any advantages in interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.

**PRE-SCREENING:** "Pre-screening" for IRB purposes is the term used to describe activities prior to obtaining Informed Consent and may not include any research procedures. Pre-screening of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for and interest in a study is a common strategy in the recruitment process. As opposed to "[Screening](#)" which for IRB purposes is considered the activities performed after obtaining consent to ensure subjects are qualified for the study and generally includes procedures e.g., lab work. [Screening](#) may not occur prior to Informed Consent.

**PREGNANCY:** encompasses the period of time from implantation until delivery. A woman shall be assumed to be **pregnant** if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

**PRINCIPAL INVESTIGATOR (PI):** The scientist or scholar with primary responsibility for the design and conduct of a research project. (See also: Investigator)

**PRISONER:** An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution. Note that this includes adjudicated youth.

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

**PROSPECTIVE STUDIES:** Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.

**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. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

**PUBLIC SERVICE ANNOUNCEMENT:** A public service announcement is generally a non-profit organization or government broadcast on radio or television, ostensibly for the public good. Public service announcements are intended to modify public attitudes by raising awareness about specific issues. Although technically it would be difficult to convince a newspaper, radio or television station that information concerning a research study constitutes raising public awareness or was intended for the public good, recruitment advertising activities that must be review by the IRB prior to use include posted notices, paid and unpaid newspaper solicitations or magazine advertisements (which may include public service announcements), websites, radio or television advertisements (which may include public service announcements).

**QUORUM** The minimal number of members of IRB who must be present for valid transaction of business.

**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.”

**REIMBURSEMENT:** Reimbursement is for expenses and generally requires justification/verification of the expense and should be available to all but may be different for each subject in contrast to [compensation](#) which is usually required to be the same for each subject as payment for participation in research.

**RESEARCH:** A systematic investigation (i.e., the gathering and analysis of information) designed to develop or contribute to generalizable knowledge.

**RESPECT FOR PERSONS:** An ethical principle discussed in the Belmont Report requiring that individual autonomy be respected and that persons with diminished autonomy be protected.

**RETROSPECTIVE STUDIES:** Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.

**RISK:** The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk."

**SCREEN FAILURE:** Subject removed from the study during the screening process because they do not meet all inclusion and exclusion criteria, or whatever other requirements must be met for research participation. Subjects who leave the study after randomization or assignment to study treatment should be counted as withdrawals rather than screen failures, even if the subject didn't start the study treatment.

**SCREENING:** "Screening" for IRB purposes is considered the activities performed after obtaining consent to ensure subjects are qualified for the study. Screening may not occur prior to Informed Consent. In contrast, "[Pre-screening](#)" for IRB purposes is the term used to describe activities prior to obtaining Informed Consent and may not include any research procedures. [Pre-screening](#) of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for and interest in a study is a common strategy in the recruitment process.

**SERIOUS ADVERSE EVENT:** (based on OHRP definition) is any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

**SERIOUS NONCOMPLIANCE:** Noncompliance that may: adversely affect subject safety or the safety of others; increase risks to subjects; violate the rights and welfare of participants (any of which may also be an unanticipated problem). Serious noncompliance may affect the subject's willingness to participate in research or may affect the integrity of the data (which may also be scientific misconduct).

- Serious noncompliance is a noncompliant event that may impact the subject safety, increase risks to the subjects, affect the integrity of the data, violate a subject's rights or welfare or affect the subject's willingness to participate in the study.

**SINGLE MASKED DESIGN:** In a single masked design, the subject does not know the treatment assignment but the investigator does.

**SITE VISIT:** A visit by agency officials, representatives, or consultants to the location of a research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

**SPONSOR:** Sponsors are the agencies, institutions, companies, organizations, foundations, or individual grantors responsible for the initiation, management, or financing of a research study. The term sponsor is understood to include any intermediaries, such as contract research organizations or coordinating centers, acting as agents of the sponsor in carrying out the responsibilities above. All research falling under these types of agreements is considered sponsored research.

**SUBJECTS (HUMAN):** "Participant" is the preferred term since it more correctly portrays the participatory aspects of social science research. Sometimes "subject" more accurately describes the role.

**SUBSTANTIVE CHANGES:** Substantive changes are changes that adversely impact the overall risk-benefit relationship for the subjects of the research.

**SURVEYS:** Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

**SUSPENSION OF RESEARCH:** A suspension of IRB approved research that is required by the IRB, IRB Director, IRB Chair or designee, or Institutional Official results in a temporary cessation of some or all of the research activities. Research may be suspended: 1) if it is not being conducted in accordance with the IRB approval; 2) when the continuation of the research may adversely affect the rights and welfare of research subjects; or 3) when continuation may represent an immediate threat of harm to the subjects.

(Note: A cessation of some or all research activities voluntarily initiated by the Principal Investigator or sponsor is not considered suspension of research.)

**TERMINATION OF RESEARCH:** A termination of IRB approval required by the IRB that results in a permanent cessation of all research activity. Research may be terminated: 1) if it is not being conducted in accordance with the IRB approval; 2) when the continuation of the research may adversely affect the rights and welfare of research subjects; or 3) when continuation may represent an immediate threat of harm to the subjects.

(Note: Cessation of all research activities resulting from the PI's decision to inactivate the study is not considered termination of research. Withdrawal of institutional support for research that results in cessation of all research activities is not considered termination of research.)

**UNDUE INFLUENCE:** Belmont states that undue influence occurs “through the offer of excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance” (National Commission, 1978, p.8). It also argues that “unjustifiable pressures” occur when “persons in positions of authority ... urge a course of action for a subject.” This includes manipulating a prospective subject's choice by utilizing the “influence of a close relative.” Lastly issues may be raised as potential undue influence when judgment may be compromised by financial incentives especially when the subject is not the recipient of the financial incentive.

- Undue influence needs to be distinguished from coercion for the purposes of NYCC IRB applications of policy. Coercion is considered the use of a threat of harm or punishment to influence behavior; e.g., in general, payments do not constitute coercion per se.
- There are also less apparent examples of vulnerability to undue influence such as Institutional vulnerability and Deferential vulnerability to undue influence.
  - ✓ Institutional is when an individual is subject to the formal authority of others which could influence the subject's participation. Examples- prisoners, military personnel, students, employees.
  - ✓ Deferential is similar to institutional but arises from informal relationships characterized by inequities in social status (gender, race, class) power or knowledge (doctor-patient relationship), or cognitive ability (elderly person defer to adult kids).

**UNEXPECTED ADVERSE EVENT:** is any adverse event, the nature, severity, or frequency of which is not consistent with either:

- (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol related documents, such as the IRB-approved research protocol, any

applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts;

**Or**

(2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event

**UNANTICIPATED PROBLEM INVOLVING RISK TO SUBJECTS OR OTHERS:** Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

(1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

(2) definitely related or probably related to participation in the research; and

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

**VIABLE:** As it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

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

**WITHDRAWAL:** A subject who signed an informed consent form but does not complete the entire study. Regardless of the reason for withdrawal, both subject-initiated decisions to withdraw and investigator- or sponsor- initiated withdrawals should be included in the reported number of withdrawals.

- i) Noncompliance is defined as any violation of any regulation that governs human subject research, any deviation from the study protocol approved by the IRB; or any violation of any conditions imposed by the IRB on the approved study or conduct of the research.

- ii) Minor noncompliance is a noncompliant event that does not impact the subject safety , compromise the integrity of study/data, violate a subject's rights or welfare or affect the subjects willingness to participate in the research. Minor noncompliance may be reported through the policies governing exeptions and deviations or by contacting the Research Department if there are questions as to how it should be reported.
- iii) Serious noncompliance is a noncompliant event that may impact the subject safety, increase risks to the subjects, affect the integrity of the data, violate a subject's rights or welfare or affect the subject's willingness to participate in the study.
- iv) Continuous noncompliance is defined as a series of more than one noncompliant event, in reasonably close proximity, that indicates the need for evaluation of the methods and systems used to protect human subjects. Continuous noncompliance need not involve a sequence of similar events if the events, taken as a whole, indicate that examination of the methods and systems used is warrented.