50. NSR studies may qualify for expedited review by the IRB if they meet the general requirements for expedited review. (See Chapter 9.)

**Review Procedures.** The following procedures govern review of investigational devices by the IRB.

1. If the IRB determines, or concurs with the assessment of the sponsor, that a device study involves a SR, then it would be governed by all of the requirements in the IDE regulations at 21 C.F.R. § 812. The IRB will document its decision that a device study involves a SR in the IRB file. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The The IRB may review any of the following materials:
   - A description of the device;
   - Reports of prior investigations conducted with the device;
   - The proposed investigational plan;
   - A description of subject selection criteria;
   - Monitoring procedures;
   - The sponsor risk assessment and the rationale used to make the sponsor's risk determination; and
   - The IRB may also request additional information if necessary from the sponsor or investigator or consult with the FDA.

A device study that is deemed to involve a NSR may begin without the submission of an IDE application to the FDA. The IRB will document its decision that a device study involves a NSR in the IRB file. Once the IRB concurs or determines that a device is NSR, the study may be conducted in accordance with the "abbreviated requirements" of the IDE regulations (21 C.F.R. §812.2(b)). The sponsor must:

(i) Label the device in accordance with 21 C.F.R. § 812.5;

(ii) Obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under 21 C.F.R. Part 50 and documents it, unless documentation is waived by the IRB under 21 C.F.R. § 56.109(c);

(iv) Comply with the requirements of 21 C.F.R. § 812.46 with respect to monitoring investigations;

(v) Maintain the records required under 21 C.F.R. § 812.140(b) (4) and (5) and make the reports required under 21 C.F.R. § 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensure that participating investigators maintain the records required by 21 C.F.R. § 812.140(a)(3)(i) and make the reports required under 21 C.F.R. § 812.150(a) (1), (2), (5), and (7); and

(vii) Comply with the prohibitions in 21 C.F.R. § 812.7 against promotion and other practices.

(iv) **Radiology Devices and Radioactive Materials.** The FDA is responsible for regulating radiology devices and radioactive materials used in health care and research. Oversight in this area is handled by The Methodist Hospital Radiation Safety Committee. (See 21 C.F.R. §§ 1000-1050).

**f. Investigators' Responsibilities for Reporting to the IRB**

The following reporting responsibilities are applicable to investigations involving drugs, biologics and devices.

(i) **Investigators' Duty to Report Adverse Events.** Principal Investigators are required to report to the IRB any adverse event occurring in research conducted at TMH or TMHRI facilities or by their employees or agent that is reported to the research sponsor or the FDA. (See below for drug and device specific requirements).

(ii) **Investigators' Duty to Forward Sponsor or Cooperative Group Safety Reports.** Investigators are required to forward safety reports (or other information concerning adverse events) issued by sponsors or cooperative groups to the IRB within 10 working days of receipt. Each report should be accompanied by the completed IRB Adverse Event/Unanticipated Problem Reporting Form.

(iii) **Investigators' Duty to Forward DSMB Reports.** Investigators are required to forward DSMB reports to the IRB within 5 working days of receipt. When a DSMB is employed, an IRB conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

(iv) **Progress Reports.** Principal Investigators are required to submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(v) **Final Report.** The Principal Investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(vi) **Duty to Notify the IRB of Serious or Continuing Noncompliance.** Whether involved in the research or not, all employees and agents of Methodist and TMHRI are required to notify an IRB if they become aware of any serious or continuing noncompliance with human subject regulatory requirements or with the determinations of the IRB.

(vii) **Investigators' Duty to Report Unanticipated Problems.** Investigators are required to report to the IRB any unanticipated problems involving risks to subjects or others that occur in research conducted at TMH or TMHRI facilities or by their employees or agents.

(viii) **Informed Consent.** If a Principal Investigator uses a drug, biologic or device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(ix) **Other**. A Principal Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(x) **Drug/Biologic Related Reports**

- **Investigators' Duty to Report Serious Adverse Events.** Investigators are required to report promptly to the IRB (using the Adverse Event/Unanticipated Problem Reporting Form) any serious adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the Principal Investigator shall report the adverse effect immediately. 21 C.F.R. § 312.64(b) See TMHRI Procedure RE43.

- **Deviations from the Investigational Plan**. Principal Investigators are required to report to the IRB all changes in the research activity and seek approval for such changes prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects. 21 C.F.R. § 312.68.

- **Other**. Principal Investigators are required to notify the sponsor and the reviewing IRB of any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.

(xi) **Device Related Reports**

- **Unanticipated Adverse Device Effect**: An Unanticipated Adverse Device Effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. 21 C.F.R. § 812.150(a)(1). Investigators are required to report Unaticipated Adverse Device Effects in accordance with TMHRI Procedure RE43.

- **Deviations from the Investigational Plan.** A Principal Investigator shall notify the sponsor and the IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval by FDA and IRB in accordance with 21 C.F.R. § 812.35(a) also is required.

**g. Sponsor's Reporting Responsibilities**

Sponsors and sponsor-investigators have the following reporting responsibilities under FDA regulations:

**(i) Drug/Biologic Related Reports**

- Sponsors and sponsor-investigators are required to promptly review all information relevant to the safety of the drug or biologic obtained or otherwise received by the sponsor or sponsor-investigator from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to FDA by the sponsor or sponsor-Investigator.

- Sponsors and sponsor-investigators are required to notify FDA and all participating investigators of any adverse experience associated with the use of a drug or biologic that is both serious and unexpected as soon as possible but in no event later than 15 calendar days after the sponsor or sponsor-investigator determines it to be reportable. The FDA should be notified by telephone, facsimile, or in writing as soon as possible but in no event later than seven calendar days of the sponsor or sponsor-investigator's receipt of the information of any unexpected fatal or life-threatening experience.

- A sponsor or sponsor-investigator who determines that its investigational drug presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur no later than 5 working days after the sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

  If the terminated investigation involves an investigational drug, the Sponsor or sponsor-investigator must assure the return of unused supply from each individual investigator whose participation in the investigation is discontinued or terminated.

**(ii) Device Related Reports**

- The sponsor/sponsor-investigator is required to report serious, unexpected adverse device effects to the FDA, to all participating investigators, and to the IRB within 10 working days of the sponsor's receipt of the information.

- Sponsors and sponsor-investigators are required to promptly investigate all safety information received and submit any relevant information to the IRB as soon as available.

- •Sponsors and sponsor-investigators shall immediately conduct an evaluation of any unanticipated adverse device effect.

- •A sponsor or sponsor-investigator who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect.

If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval.

The sponsor or sponsor-investigator must assure the return of unused supply from each individual investigator whose participation in the investigation is discontinued or terminated.

### h. Off-Label (Unapproved) Use of FDA-Regulated Products in Medical Practice Versus Research

Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (*i.e.*, off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

- Off-label use of a legally marketed product in this manner when the intent is solely the **practice of medicine** does ***not*** require IRB review or the submission of an IND or IDE.
- The FD&C Act's Practice of Medicine Exemption states: "Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a

determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices."

- Off-label use of a marketed product in **research** (*i.e.*, as part of an investigation designed to develop or contribute to generalizable knowledge) does require IRB review, unless the research does not involve human subjects.
- Off-label use of a marketed product intended to support a marketing application (*e.g.* for **a change in labeling)** requires both IRB review and submission of an IND or IDE.

**i. Treatment Use of Investigational Drugs and Medical Devices**

Treatment IND and IDE studies require prospective IRB review, informed consent and FDA approval. Although the sponsor may apply for a waiver of local IRB review under a treatment IND or IDE, such a waiver does not apply to the informed consent requirement. It is the policy of TMHRI that all treatment IND or IDE studies must be reviewed and prospectively approved by the IRB. See TMHRI Official Procedure RE-03.

**(i) Drugs and Biologics**

The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. Where necessary, this mechanism can be used even for providing such drugs to a single patient-subject. The treatment IDE is a comparable mechanism for providing investigational devices to such patient-subjects.

The FDA regulations at 21 C.F.R. §§ 312.34 and 312.35 specify the requirements that must be satisfied before a treatment IND can be issued. TMHRI Official Procedure RE-03 also should be consulted for more specific requirements.

- **Treatment IND.** During the clinical investigation of a drug, it may be appropriate to use the drug in treatment of patients not in the clinical trials. Such use requires FDA approval under a treatment protocol (*see* 21 C.F.R. 312.35 and TMHRI Official Procedure RE-03) or a treatment IND (21 C.F.R. § 312.34), as well as IRB review and approval and informed consent.

- **Single Patient Treatment IND.** The Single-Patient Treatment IND is not described in regulations yet, but was added to the law under the FDA Modernization Act ("FDAMA") in 1997. From an operational standpoint, the Single-Patient IND must meet the same requirements as a standard IND, and requires prospective IRB review and approval, informed consent, and FDA approval.

- **Group C Treatment IND.** Group C drugs are Phase 3 study drugs that have shown evidence of efficacy in a specific tumor type. Group C drugs are

distributed by the National Cancer Institute ("NCI") with a Guideline Protocol and an informed consent document. Informed consent is required, and although FDA and NCI permit the use of Group C drugs without local IRB review, Methodist policy normally requires review and approval by a Designated IRB. Investigators who are considering use of Group C drugs should contact the IRB Chairperson for guidance.

- **Orphan Drugs.** The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The treatment use of an orphan drug for a serious or immediately life-threatening disease condition requires prospective IRB review and approval and informed consent. 21 C.F.R. §§ 316.40 and 312.34.

- **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies are conducted under the auspices of a treatment IND and require prospective IRB review and informed consent, as well as FDA approval.

**(ii) Devices**

**Treatment IDE.** Treatment use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. The FDA regulations at 21 C.F.R. § 812.36 specify the requirements that must be satisfied before a Treatment IDE canbe issued. TMHRI Official Procedure RE-03 also should be consulted for more specific requirements. Such use may occur when: (i) the patient has a serious or immediate life-threatening condition; (ii) there is no comparable or satisfactory alternative available; (iii) the device is under investigation in a controlled trial for the same use (or such trials have been complete); (iv) the sponsor is pursuing marketing approval/clearance; and (v) the sponsor has submitted and the FDA has approved an IDE under 21 C.F.R. § 812.36. Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required. FDA approval also is required.

**j. Gene Transfer Research**

Gene transfer research involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by both the FDA and the NIH Office of Biotechnology Activities ("OBA"), as well as OHRP.

- FDA regulations require the submission of an IND for human gene transfer research.
- No individual may be enrolled in human gene transfer research until review has been completed by the Recombinant DNA Advisory Committee ("RAC") at NIH;

approval of TMHRI Institutional Biosafety Committee(s) has been obtained; IRB approval has been obtained; and the investigator has obtained all other regulatory authorizations (such as any consents required by regulations) from the subject (65 Fed. Reg. 196, October 10, 2000).

- While the RAC is advisory to the Director of NIH, compliance with its guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA

> ***Note: Regardless of the presence of NIH funds, it is the policy of TMHRI that all human gene transfer research to be performed at Methodist shall undergo RAC review prior to completion of institutional approval(s) and commencement of research activities.***

**k. Emergency Use of a Test Article without IRB Review**

An exemption under FDA regulations at 21 C.F.R. § 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval. TMHRI Official Procedure RE-02 also should be consulted for more specific requirements.

**(i) TMHRI Requirements.** If at all possible, TMHRI policy requires that investigators consult the IRB Chairperson for guidance when considering the emergency use of drugs or medical devices.

**(ii) Emergency Use of Drugs.** Emergency use of an investigational new drug occurs when the emergency situation does not allow time for submission of an IND. All of the following conditions must be met for this type of emergency use:

1. A human subject is in a life-threatening situation;
2. No standard acceptable treatment is available;
3. There is insufficient time to obtain IRB approval;
4. The emergency use must be reported to the IRB within five working days (such reporting must not be construed as IRB approval for the emergency use); and
5. Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below.

Use of the drug also requires a request to FDA to authorize shipment of the drug for the emergency use. Such authorization is conditioned on the sponsor making an appropriate IND submission as soon as practicable (21 C.F.R. § 312.36). TMHRI Official Procedure RE-02 also should be consulted for more specific requirements.

The emergency use of an investigational new drug may take place without IRB review and approval, provided that the use is reported to the IRB within 5 working days. Informed consent is required unless the situation is life-threatening, the criteria at 21 C.F.R. § 50.23(a) or 50.23(b) have been met, and the IRB is notified within 5 working days. See TMHRI Official Procedure 02, RE-02 for additional information.

**(iii) Emergency Use of Devices.** Emergency use of an unapproved device may occur in an emergency situation when (i) an IDE for the device does not exist, (ii) a physician wants to use a device in a way not approved under an existing IDE, or (iii) when a physician is not an investigator under the existing IDE.

The device may be used if (i) the patient has a life-threatening condition that needs immediate treatment, (ii) there is no generally acceptable alternative treatment, and (iii) there is no time to obtain FDA approval. Such uses require as many of the following patient protections as possible (see FDA Center for Devices and Radiological Health Guidance on IDE Policies and Procedures, January 20, 1998): (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB chairperson (this concurrence does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization from the IDE sponsor (if an IDE exists) Follow-up reports should be provided to the Sponsor if an IDE exists, or to FDA if no IDE exists. Such use is limited to a few patients.

**l. Emergency Use of a Test Article without Informed Consent**

An exception under FDA regulations at 21 C.F.R. § 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certifies in writing all of the following specific conditions:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article;

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject;

(3) Time is not sufficient to obtain consent from the subject's legal representative; and

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

In addition,

(5) If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within five working days; and

(6) The emergency use must be reported to the IRB within five working days (such reporting must not be construed as IRB approval for the emergency use).

TMHRI Official Procedure RE-02 also should be consulted for more specific requirements.

**TMHRI Requirements.** If at all possible, TMHRI policy requires that investigators

consult the IRB Chairperson for guidance when considering the emergency use of drugs or medical devices.

**m. Compassionate Use of Investigational Drugs and Devices**

"Compassionate Use" is not a term that appears in the FDA or DHHS regulations or the Common Rule.

For studies involving investigational drugs, "Compassionate Use" is often meant to refer to the emergency use situations discussed above.

For studies involving investigational devices, compassionate use may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious disease or condition who does not qualify for the trial. Such uses require prior FDA approval of a protocol deviation under 21 C.F.R. § 812.35(a). Prior FDA approval for compassionate use should be obtained before the device is used. On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA.

Compassionate use of an unapproved device also requires as many of the following protections as possible: (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB Chairperson (which does not constitute IRB approval; (iv) an independent assessment of an uninvolved physician; and (v) authorization of the IDE sponsor. Follow-up reports should be provided to the Sponsor. Such use may involve an individual patient or a small group of patients. See IMHRI Official Procedure 02, RE-02.

IMHRI Requirements: If at all possible, IMHRI policy requires that investigators consult the IRB Chairperson for guidance when considering such "compassionate use."

**NOTE:** The above "Compassionate Use" situations should not be confused with the Humanitarian Use Device ("HUD") Exemption (see item "n" below).

**n. Humanitarian Device Exemptions**

A HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission of a humanitarian device exemption ("HDE") application. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use. The labeling for a HUD must state that the device is a humanitarian use device and that, although the device is authorized by federal law, the effectiveness of the device for the

specific indication has not been demonstrated.

An approved HDE authorizes marketing of the HUD. However, a HUD may only be used after approval of the convened (full) IRB has been obtained for use of the device at the institution for the FDA-approved indication. 21 C.F.R. § 814.124(a). After granting initial approval, the IRB may use expedited procedures for conducting continuing review. Informed consent of patients is not required because an HDE provides for marketing approval, so use of the HUD does not constitute research. TMHRI Official Procedure RE-01 also should be consulted for more specific requirements.

**(i) On-Label Use**

If a Principal Investigator or physician in an emergency situation determines that approval from an IRB cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the applicable IRB. In such an emergency situation, the physician shall, within 5 days after the use of the device, provide written notification to the Chairman of the IRB of such use. Such written notification shall include the identification of the patient involved, the date on which the device was used, and the reason for the use.

**(ii) Off-Label Use**

A HUD may be used off-label for emergency purposes, i.e., to save the life or protect the physical well-being of a patient, so long as patient protection measures, as described below, are followed.

1. Before the emergency use occurs: If possible, the physician should obtain:
   a. Concurrence from the chair of the IRB;
   b. Informed consent from the patient or his/her legal representative;
   c. An independent assessment by an uninvolved physician; and
   d. Authorization from the HDE holder.

2. After the emergency use occurs the physician or investigator must submit a follow-up report on the patient's condition and information regarding the patient protection measures to the HDE holder and the applicable IRB.

**n. Planned Emergency Research**

An exception under FDA regulations at 21 C.F.R. § 50.24 permits planned research in an emergency setting without the informed consent of the subjects.

Planned emergency research that is not FDA-regulated is also permitted by DHHS and the Common Rule when specific Department or Agency action is taken to exercise the waiver provision at 45 C.F.R. § 46.101(i). However, planned emergency research is usually subject to FDA regulations because it usually involves use of an FDA-regulated test article. When this is the case, the FDA requirements govern, and no notification of OHRP is required.

The requirements for planned emergency are extremely complex and require much consultation within TMHRI, within the community in which the research will be conducted, and within FDA, DHHS, or other Common Rule Agency. Investigators should contact the IRB chairperson well in advance if they wish to conduct planned emergency research.

***It is the responsibility of the IRB Chairperson to provide prompt written notification to the TMHRI Institutional Official, the TMHRI Department of Legal Services, and the TMHRI Research Protection Officer should the TMHRI IRB receive a proposal for planned emergency research.***

## Chapter 13.
## Social and Behavioral Research

Social and behavioral research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention.

**a. Social and Psychological Harms.** When evaluating social and behavioral science research, the IRB will carefully examine the research to determine the probability of risk of harm to subjects.

(i) The IRB will consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.

(ii) The IRB will also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social relationships.

(iii) Collecting any identifiable, private information about any living individual generally constitutes human subject research. If information is being collected on living individuals in addition to the primary "target" subjects, the IRB will consider the risk of harm to those "non-target" individuals, as well. The IRB may require additional protections, study redesign, or the informed consent of "non-target" individuals (unless the requirement for informed consent can be waived).

In order to mitigate such harms, the IRB will review the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in the research.

**b. Privacy and Confidentiality Concerns.** The use of confidential information is an essential element of much social and behavioral research.

(i) It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not inappropriately invade the privacy of the individual. In general, identifiable information may not be obtained from private (nonpublic) records without the approval of the IRB and the informed consent of the subject. Such is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that will allow an exemption from IRB approval and informed consent to be granted, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements.

(ii) It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected in order to prevent a breach of confidentiality that potentially could harm subjects.

**c. Safeguarding Confidentiality.** When information linked to individuals will be recorded as part of the research design, the IRB should ensure that adequate precautions exist to safeguard the confidentiality of the information. The more sensitive the data

being collected, the more important are the confidentiality procedures.

(i) If the IRB reviews survey and interview research, it will be particularly aware of the regulatory provision at 45 C.F.R. § 46.117(c)(1) for waiving documentation of consent when a signed consent form would itself constitute a risk to the subjects.

(ii) Among the available methods for ensuring confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

(iii) Federal regulations at 45 C.F.R. § 46.116(a)(5) require that subjects be informed of the extent to which confidentiality of research records will be maintained.

(iv) Federal officials have the right to inspect research records, including consent forms and relevant clinical records of individual subjects, to ensure compliance with the rules and standards of their programs.

(v) The IRB may require that an investigator obtain a DHHS CoC. A CoC protects against the compelled disclosure of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

**d. Exempt Research.** The IRB, not the individual investigator, makes the determination as to whether research is exempt from IRB review. If the Principal Investigator believes that the study he or she is planning is exempt from IRB review, he or she should submit to the IRB the form for verification of exemptions.

All exemptions claimed for research conducted at Methodist or by employees or agents of Methodist must be verified by the IRB. The exemptions addressed in e, f and g below are particularly applicable to social and behavioral research

**e. Exempt Research in Educational Settings.** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from Federal regulations in accordance with 45 C.F.R. § 46.101(b)(1).

(i) This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed

(ii) Even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected.

(iii) When educational institutions become engaged in the actual conduct of research, they are required to file an Assurance in accordance with Federal regulations at 45 C.F.R. § 46.103(a).

**f. Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or The Observation of Public Behavior.** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at 45 C.F.R. § 46.101(b)(2).

(i) When the subjects are **adults**, this exemption applies **UNLESS**:

(a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); **AND**

(b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. **NOTE:** The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information recorded is both identifiable and sensitive, except in the case of children as follows.

(ii) This exemption applies to research involving **children, EXCEPT** that: (a) research involving survey or interview procedures with children is **NOT EXEMPT**; and (b) research involving observation of the public behavior of children is **NOT EXEMPT** if the investigator participates in the activities being observed.

(iii) If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) federal statutes require confidentiality without exception. **NOTE**: Condition (b) regarding federal statutes rarely applies.

(iv) If not exempt under the conditions described above, the IRB may often utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior.

**g. Exempt Research using Existing Data and Documents.** Social and behavioral research often relies on analysis of existing data or documents. Such research, which may be exempt, is addressed in the next chapter.

**h. Expedited IRB Review of Social and Behavioral Research.** Social and behavioral research may receive expedited review if it presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998 Federal Register List of Categories of Research that may be Reviewed by Expedited Review.

> The categories discussed below are particularly applicable to social and behavioral research, and include research involving children as well as adult subjects. However, these categories do NOT apply to research involving prisoners.

**i. Expedited Review of Research Involving Existing Data and Documents (Expedited Category #5).** Research involving materials (including data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes, may be reviewed using expedited procedures.

(i) Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.

(ii) Non-exempt research involving materials that will be collected in the future for a non-research purpose.

j. **Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes (Expedited Category #6).** The IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes

k. **Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies (Expedited Category #7).** The IRB may utilize expedited procedures to review the following:

(i) Research on individual or group characteristics or behavior; or

(ii) Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

This category covers a wide range of non-exempt social and behavioral research activities when they present no greater than minimal risk to subjects. Examples include, but are not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior.

l. **Research Involving Deception.** If the IRB reviews research involving incomplete disclosure or outright deception, the IRB must apply both common sense and sensitivity to the review.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects will be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a countervailing benefit.) The IRB should also make sure that the proposed subject population is suitable.

Deception is only permitted where the IRB documents that waiver of the usual informed consent requirements is justified under the criteria present in Federal regulations at 45 C.F.R. § 46.116(d). Specifically, the IRB must find and document that all four of the following criteria have been satisfied:

(i) The research presents no more than minimal risk to subjects;

(ii) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(iii) The research could not practicably be carried out without the waiver or alteration; and

(iv) Where appropriate, the subjects will be provided with additional pertinent information after participation.

Note that the regulations make no provision for the use of deception in research that poses greater than minimal risk to subjects.

## Chapter 14.
## Bio-Social and Bio-Behavioral Research

Many studies combine characteristics of behavioral and social research with characteristics of biomedical research. Such studies may be referred to as bio-social and bio-behavioral research. The IRB must review such studies to determine whether they may be exempt under the DHHS regulations. "Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens" may be exempt under 45 C.F.R. § 46.101(b)(4) "if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects."

a. **Prospective Use of "Existing" Materials.** Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents, records or specimens) that will be collected prospectively for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under DHHS regulations at 45 C.F.R. § 46.101(b)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated. Under some circumstances, the IRB may use expedited procedures to review such research.

**b. Retrospective Use of Existing Materials.** Retrospective studies are research studies that involve the review of materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated. Such research may be exempt under DHHS regulations at 45 C.F.R. § 46.101(b)(4) if the information is publicly available or if the information is recorded in such a manner that **subjects cannot be identified, either directly or through identifiers linked to the subjects**. If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects. Retrospective studies using existing materials that are not exempt and entail greater than minimal risk require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited reviewer indicates concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

**c. Research Utilizing Large Existing Data Sets.** Bio-social research and bio-behavioral research often involve the use of large, existing data sets. When the datasets are publicly available (i.e., available to the general public, with or without charge), their use is exempt.

The use of existing data sets that are not publicly available generally requires IRB review if they contain identifiable private information about living individuals. In such cases,

the IRB must determine whether the information can be used without additional informed consent from the subjects. Alternatively, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. In this situation, codes and other identifiers are permanently removed from the data set before the investigator receives the data, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities. An alternative to anonymizing data is to maintain the data set as a data repository under conditions established by OHRP.

**d. Research Utilizing Data or Tissue Repositories.** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute potentially identifiable human tissue materials for research purposes. TMHRI Official Policy RE-27 governs tissue banking.

Repository activities involve three components: (i) the **collectors** of data or tissue samples; (ii) the **repository** storage and data management center; and (iii) the **recipient** investigators.

Under a repository arrangement, the IRB oversees all elements of repository activity, setting the conditions for collection, storage, secure maintenance, and sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the conditions under which data and/or tissues (which are identifiable within the repository) may be shared, such that additional informed consent of the tissue donors is not required.

Typically, these conditions involve formal, written agreements stipulating as follows:

(i) The repository will not release any identifiers to the investigator;
(ii) The investigator will not attempt to recreate identifiers, identify subjects, or contact subjects;
(iii) The investigator will use the data only for the purposes and research specified;
(iv) The investigator will comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects. Additional information about the operation of data repositories can be found on the OHRP website; and;
(v) The investigator will not present results in a manner that would allow subjects to be identified.

**e. Epidemiological Research.** Epidemiological research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research.

Epidemiological studies often present significant problems regarding both **privacy** and

**confidentiality**. The IRB must first consider privacy issues, and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. The IRB should seek to establish that the investigator's access to any identifiable information that is to be utilized is authorized and justified. Once the IRB's privacy concerns have been resolved, the IRB should examine mechanisms for maintaining the confidentiality of data collected. Because epidemiological research typically requires very large numbers of subjects, epidemiology investigators almost always request that the IRB waive the usual requirements for informed consent. In order to approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met. See 45 C.F.R. § 46.116(d).

f. **Issues in Genetic Research.** Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic information can adversely affect an individual's insurability and employability.

The IRB must be particularly careful about approving research that appears to involve only a simple, minimal risk blood draw, but then goes on to include or add a component involving genetic analysis. The addition of the genetic analysis can radically alter the level of risk.

g. **Family History Research.** Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member (called a proband) about other family members. The family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them. The IRB should determine whether family members are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 45 C.F.R. § 46.116(d).

h. **Research Involving Potentially Addictive Substances.** Research involving potentially addictive substances often involves the use of what may be termed "abuse-liable" substances. Abuse-liable substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both legal and illicit drugs.

The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:

(i) The IRB should consider the subject's capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced;
(ii) If such research involves subjects that are institutionalized, the subject's ability to exercise autonomy could be impaired;
(iii) The IRB should also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or overselected;
(iv) The IRB should be sensitive to the ethical context of the research, in that there

may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs; and.

(v) The IRB should focus on the considerations of risk and benefit of such research.

## Chapter 15.
## Potentially Vulnerable Subject Groups

DHHS regulations at 45 C.F.R. § 46.111(b) and 45 C.F.R. Part 46, Subparts B, C and D, and FDA regulations at 21 C.F.R. § 56.111(b) require the IRB to give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, fetuses and neonates, mentally disabled persons, and economically or educationally disadvantaged persons.

The IRB is required to include adequate representation to consider specific kinds of research involving these vulnerable populations in a satisfactory manner.

**a. Elements to Consider.** The IRB should pay special attention to the following specific elements of the research plan when reviewing research involving vulnerable subjects:

(i) Issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and voluntarism; coercion and undue influence; and confidentiality of data;

(ii) The IRB should carefully consider group characteristics, such as economic, social, physical, and environmental conditions, so that the research incorporates additional safeguards for vulnerable subjects;

(iii) Investigators should not over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population;

(iv) Investigators must be knowledgeable about applicable laws that bear on the decision-making abilities of potentially vulnerable populations;

(v) Research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB should look to see that such procedures are a part of the research plan;

(vi) In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly to gauge their understanding paragraph by paragraph; and

(vii) In appropriate circumstances, the IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB, that a designated individual oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

**b. Pregnant Women, Human Fetuses and Neonates.** DHHS regulations at 45 C.F.R. Part 46, Subpart B detail special protections for research involving pregnant women, human fetuses and neonates. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent.

Unilateral exclusion of non-pregnant women of reproductive potential from research, in order to avoid a risk, should not be permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

Four separate categories, each with its own requirements and IRB determinations, apply to research with pregnant women, human fetuses and neonates, as outlined below. IRB determinations regarding the applicable category and protocol-specific findings relative to the specific requirements of the relevant category should be clearly documented in IRB records. DHHS regulations at 45 C.F.R. Part 46 provide the following in pertinent part:

**§ 46.204 Research involving pregnant women or fetuses prior to delivery.**

Pregnant women or fetuses prior to delivery may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is not greater than minimal, or any risk to the fetus which is greater than minimal is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) The woman's consent or the consent of her legally authorized representative is obtained in accord with the informed consent provisions of subpart A of this part, unless altered or waived in accord with §46.101(i) or §46.116(c) or (d);

(e) The woman or her legally authorized representative, as appropriate, is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child;

(f) For children as defined in 45 C.F.R. § 46.402(a) who are pregnant, assent and permission are obtained in accord, with the provisions of subpart D of this part;

(g) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(h) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(i) Individuals engaged in the research will have no part in determining the viability of a fetus.

**§ 46.205 Research involving fetuses after delivery.**

(a) After delivery, fetuses may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to fetuses.

(2) The individual(s) providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child.

(3) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.

(4) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.

(5) Individuals engaged in the research will have no part in determining the viability of a fetus.

(6) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Fetuses of uncertain viability. After delivery, and until it has been ascertained whether or not a fetus is viable, a fetus may not be involved in research covered by this subpart unless the following additional conditions are met:

(1) The IRB determines that:
(i) The research holds out the prospect of enhancing the probability of survival of the particular fetus to the point of viability, and any risk is the least possible for achieving the objectives or the research, or
(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no risk to the fetus resulting from the research; and
(2) The legally effective informed consent of either parent of the fetus or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, unless altered or waived in accord with §46 101(i) or §46.116(c) or (d)
(c) Nonviable fetuses After delivery, a nonviable fetus may not be involved in research covered by this subpart unless all of the following additional conditions are met:
(1) Vital functions of the fetus will not be artificially maintained;
(2) The research will not terminate the heartbeat or the respiration of the fetus;
(3) There will be no risk to the fetus resulting from the research;
(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
(5) The legally effective informed consent of both parents of the fetus is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable fetus will suffice to meet the requirements of this paragraph. The consent of a legally authorized representative of either or both of the parents of a nonviable fetus will not suffice to meet the requirements of this paragraph
(d) Viable fetuses A fetus, after delivery, that has been determined to be viable is a child as defined by §46.402(a) and may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

**§ 46.206 Research involving, after delivery, the placenta, the dead fetus, or fetal material.**
(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.
(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable

**§ 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses.**
The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46 204 only if:
(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serous problem affecting the health or welfare of pregnant women or fetuses; and
(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:
(1) That the research in fact satisfies the conditions of §46.204, as applicable, or
(2) The following:
(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women or fetuses;
(ii) The research will be conducted in accord with sound ethical principles; and
(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part, unless altered or waived in accord with §46.101(i) or §46.116(c) or (d).

**c. Research Involving Prisoners.** DHHS regulations at 45 C.F.R § Part 46, Subpart C detail special protections for research involving prisoners, who, due to their incarceration, may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. In order to consider research involving prisoners, the IRB should:

(i) Have a majority of its members not otherwise associated with the prison, and
(ii) Include a prisoner or a prisoner advocate, who can adequately represent the interests of the prisoners, unless the research has already been reviewed by an IRB that included a prisoner advocate.

IRBs that approve research involving prisoners should:

(i) Make the seven additional findings set forth in 45 C.F.R. § 46.305 that are listed below;
(ii) Determine which category in 45 C.F.R. § 46.306 permits the research to go forward; and
(iii) If the research is DHHS-supported, certify these findings to OHRP. Certification to OHRP is not required for research not supported by DHHS. However, OHRP recommends that the IRB apply the standards of Subpart C to all prisoner research. Should non-DHHS research fall outside the category stipulations under 45 C.F.R. §.46.306, OHRP recommends that the IRB consult with appropriate experts before approving the research.

Under DHHS regulations, prisoners may participate in the following categories of research:

(i) Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behavior;
(ii) Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons;
(iii) Research on particular conditions affecting prisoners as a class (providing the Secretary of HHS has consulted with appropriate experts and published the intent to support such research in the Federal Register); and
(iv) Research involving practices that have the intent and reasonable probability of benefiting the prisoner subject. If the research involves possible assignment to a control group that may not benefit from the research, the Secretary of HHS must also consult with appropriate experts and publish the intent to support the research in the Federal Register (45 C.F.R. § 46.306).

The following additional determinations must be made by the IRB before research involving prisoners goes forward (45 C.F.R. § 46.305):
(i) The research under review is limited to one of the categories of research listed above;
(ii) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared with the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
(iii) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
(iv) Procedures for selecting subjects within the prison are fair to all prisoners, and

immune from arbitrary intervention by prison authorities or prisoners. Unless the Principal Investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
(v) The information is presented in language that is understandable to the subject population;
(vi) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
(vii) Where the board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoner's sentences, and for informing participants of this fact.

**d. Research Involving Children.** DHHS regulations at 45 C.F.R. Part 46, Subpart D and FDA Regulations at 21 C.F.R. Part 50, Subpart D require special protections for research involving children. Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. The legal age of consent generally is 18 years of age in the state of Texas.

The IRB should consider three main issues when reviewing research involving children: (1) risk-benefit analysis; (2) parental permission; and (3) assent of the child.

(i) IRBs should make certain findings and determinations when reviewing research involving children. IRB records must reflect the IRB's understanding and justification for the risks and benefits posed by approved research involving children. Proposed research must fall within one of the following four categories:
(a) Research not involving greater than minimal risk;
(b) Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects;
(c) Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition; and
(d) Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
Each category entails specific conditions that must be met before the proposed research can be approved.

The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining when children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular

protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement where (a) the research involves no more than minimal risk; (b) the waiver will not adversely affect subjects' rights and welfare; (c) the research could not practicably be carried out without the waiver; and (d) when appropriate, the subjects will be provided with pertinent information after participation. The IRB also may waive the assent requirement if the research otherwise meets the requirements for waiver in 45 C.F.R. § 46.116.

If it is deemed appropriate that the child's assent should be solicited, the assent form should be tailored for the child, with respect to his or her level of understanding. For young children, the assent form should be a relatively brief document, with simple, age-appropriate language, presented in a manner understandable to the child.

Children who are wards of the state or any other agency, institution or entity can be included in research approved under 45 C.F.R. §§ 46.406-46.407 only if such research meets one of the following requirements:

- the research is related to the child's status as a ward; or
- the research is conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards.

If the research is approved under the foregoing requirements, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s) or the guardian organization.

**e. Research Involving Decisionally Impaired Subjects.** Decisionally impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals who may be considered decisionally impaired, with limited decision-making ability, include, for example, individuals 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.

While there are no regulations specific to research involving cognitively impaired persons, the IRB should take special care to consider issues such as: the selection of

subjects, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis.

IRB decisions will be made in accordance with the ethical principles underlying human subject research as set forth in the *Belmont Report*

**f. Research Involving Other Potentially Vulnerable Adult Subjects.** Employees, students, and trainees at Methodist should also be considered vulnerable subjects.

The context of the research is an important consideration for the IRB to have in mind when reviewing research that involves other potentially vulnerable subjects. Research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged, for example, pose significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of subjects, and the IRB must take such considerations into account. Nevertheless, research involving these subjects is socially important for understanding and eventually improving adverse health in these populations.

**g. Fetal Tissue Transplantation Research.** Public Law 103-43 governs human fetal tissue transplantation research supported by DHHS.

**h. Research Involving Deceased Persons.** Research involving deceased persons is not covered by the FDA or DHHS human subject regulations. However, such research may be covered under applicable Texas laws. All questions regarding research with deceased persons should be addressed to the TMHRI Office of Research Protection. TMHRI Official Procedure RE-26 governs cadavers and anatomical specimens.

# Appendix A – GLOSSARY

**Adverse event** – An undesirable and unintended, although not necessarily unexpected, result arising during the course of a research protocol.

**Adverse Event Report** – Report to appropriate institutional officials about adverse events.

**ARENA** – Applied Research Ethics National Association: a membership organization for individuals interested in ethical issues relating to medicine and research.

**Assent** – Agreement by an individual not competent to give legally valid informed consent to participate in research (e.g., a child).

**Assurance** – A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with regulations governing the protection of human subjects in research. Assurance is the word used in the Federal Policy (Common Rule). Also known as Federal-Wide Assurance ("FWA").

**Autonomy** – See "Respect for Persons."

**Belmont Report** – A statement of basic ethical principles governing research involving human subjects issued in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

**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.

**Certificate of Confidentiality** – A Certificate of Confidentiality protects the compelled release of identifiable information about research subjects in any legal proceeding. These documents are issued by the DHHS and can be requested for all research, regardless of funding source [42 USC 241(d)].

**Clinical Investigation** – Any experiment that involves a test article and one or more human subjects that is subject to Food and Drug Administration (FDA) requirements for research or marketing permits.21 C.F.R. Part 50.3(c) and 56.102(c).

**Clinical Trial** – A controlled study involving human subjects designed to contribute to generalizable knowledge about the safety and/or effectiveness of an intervention or treatment.

**Coercion** – The act of inducing or pressuring an individual to consent to participate in

research or to stay in research.

**Cognitive Impairment** – Some disorder that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished.

**Common Rule** – The short description of the Federal Policy for the Protection of Human Subjects in Research [56 Fed. Reg. 29003].

**Competence** – The 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.

**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** – Agreement to do something. Informed consent is agreement to do something based upon a complete understanding of that task.

**Control** – 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 the study

**Continuing Review** – The regulatory requirement that the Institutional Review Board (IRB) review research at intervals not greater than one year. The IRB may review research at more frequent intervals [45 C.F.R. § 46.109(e); 21 C.F.R. § 56.109(f)].

**Data and Safety Monitoring Board (DSMB)** – A group of people who monitor a clinical trial for adverse events and other trends. The Data and Safety Monitoring Board looks for any information that might warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

**Deception** – Intentionally misleading with respect to a research protocol.

**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.

**Federal Policy** – Another short reference, along with the phrase "Common Rule," for the Federal Policy for the Protection of Human Subjects in Research. (56 Fed. Reg. 28003)

**Fetus** – The product of conception from the time of implantation until delivery. Refer to Subpart B of 45 C.F.R. Part 46 for specific findings that are required for research involving fetuses.

**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.

**Inclusion Criteria** – The criteria that establish whether a person is eligible to participate in a clinical trial.

**Incompetence** – A legal term meaning inability to manage one's own affairs.

**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, and other agencies) [45 C.F.R. § 46.102(b); and, 21 C.F.R. §§ 50.3(h) and 56.102(f)].

**Institutional Review Board (IRB)** – A review body established by regulation to protect the welfare of human subjects recruited to participate in research.

**Institutional Official** – The individual at an institution who is responsible for ensuring the effective administration and implementation of the institution's system for the protection of human subjects.

**Investigator** – The individual who actually conducts a research investigation. 21 C.F.R. §§ 50 3(d) and 56.102(h).

**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.

**Legally Authorized Representative (LAR)** – The person authorized by law to consent to something on behalf of another person. For research purposes, only select states permit a LAR to consent for research participation. 45 C.F.R. § 46.102(c); 21 C.F.R. § 50.3(e).

**Member** – A person who is listed on the roster of an IRB as a voting participant in IRB deliberations and actions.

**Minimal Risk (Federal Policy, DHHS Subpart A, and FDA)** – 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. 45 C.F.R. § 46.102(i); and, 21 C.F.R. §§ 50.3(k) and 56.102(j).

**Minimal Risk (DHHS Subpart C - prisoners)** – The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. 45 C.F.R. § 46.303(d).

**Monitoring** – A mechanism for keeping track of any part of the research process: data analysis, recruitment of subjects, informed consent process, to ensure its compliance with Institutional Review Board dictates and the federal regulations

**Normal Volunteers** – Volunteer subjects in a research study who do not have the condition under study. The 1993 Office for Protection from Research Risks (OPRR) Guidebook defines normal volunteers as follows: "Normal" may not mean normal in all respects. For example, patients with broken legs (if not on medication that will affect the results) may serve as normal volunteers in studies of metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the "normals" in a study of diabetes complicated by heart disease [OPRR IRB Guidebook, 1993, G-9]

**Oral Consent** – Typically refers to informed consent that is obtained from a subject without use of a written informed consent document.

**Office for Human Research Protections (OHRP)** – An office within the DHHS that was created in June of 2000. OHRP is responsible for the implementation of the DHHS regulations (45 C.F.R. Part 46 governing the protection of human subjects in research.

**Parental Permission** – The agreement of one or both parents or a guardian to research involving a minor. 45 C.F.R. § 46.402(c).

**Placebo** – In biomedical research, a chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than the actual power of a drug. In social and behavioral research, a condition that mimics the experimental context but does not include the experimental manipulation under study. As in biomedical research, the control condition is used to confirm that observed effects are the result of the experimental manipulation rather than the research context itself.

**Prisoner** – An individual involuntarily confined or detained 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 (4) incarcerated in a penal institution. 45 C.F.R. 46.303(c).

**Prisoner Representative** – A member of an IRB who has appropriate background and

experience to represent the interests and concerns of an individual who is involuntarily confined to an institution. 45 C.F.R. § 46.304(b).

**Privacy** – Concealment from others of information about oneself.

**Protocol** – The formal design or plan of an experiment or research activity. 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 Health Service (PHS)** – A division within the DHHS. PHS agencies include the National Institutes of Health, Centers for Disease Control, the Indian Health Service, and the Substance Abuse and Mental Health Services Administration.

**Random Assignment** – Assignment of subjects to different treatments, interventions, or conditions according to chance.

**Recruitment** – The process of enrolling human subjects in research protocols.

**Research** – Under the Federal Policy and the DHHS Subpart A, research is a systematic investigation designed to develop or contribute to generalizable knowledge. 45 C.F.R. § 46.102(d). Under FDA regulations, "research" is synonymous with "clinical investigation". 21 C.F.R. § 56.102(c).

**Respect for Persons** – A principle enunciated in the Belmont Report stating that (1) individuals should be treated as autonomous agents, and, (2) persons with diminished autonomy are entitled to protection.

**Risk** – The probability of harm or injury occurring as a result of participation in a research study.

**Secretary** – In the context of the federal regulations pertaining to the protection of human subjects in research, refers to the head of a federal agency. 45 C.F.R. § 46.102(a)].

**Sponsor** – Typically refers to the entity that initiates a clinical investigation but does not actually conduct the investigation. 21 C.F.R. §§ 50.3(e) and 56.102(j).

**Sponsor-Investigator** – An individual who both initiates and actually conducts a clinical investigation. 21 C.F.R. §§ 50.3(f) and 56.102(k).

**Subpart A** – The DHHS codification of the Federal Policy for the Protection of Human Subjects in Research is found in Subpart A of 45 C.F.R. Part 46.

**Subpart B** – Subpart B of the DHHS regulations contains additional protections for pregnant women and fetuses that are involved in research, and references human in

vitro fertilization research. 45 C.F.R. Part 46.

**Subpart C** – Subpart C of the DHHS regulations contains additional protections for prisoners who are involved in research. 45 C.F.R. Part 46.

**Subpart D** – Subpart D of the DHHS regulations [contains additional protections for children who are involved in research. 45 C.F.R. Part 46.

**Surveys** – Studies designed to obtain information from human subjects through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

**Suspension** – Typically used in the context of a federal agency taking action against an institution. For example, the Office for Human Research Protections can suspend an Assurance, preventing the institution from continuing to conduct studies supported with federal funds.

**Test Article** – Any drug, biological product for human use, medical device for human use, human food additive, color additive, electronic product subject to FDA regulations under 42 USC 262, 263b-263N (21 C.F.R. §§ 50.3(j) and 56.102(e)).

**Undue Influence** – This refers to a prohibition in the Common Rule that investigators not use unfair measures or influence to enroll persons in research. 45 C.F.R. § 46.116.

**Unanticipated Problems Involving Risks to Subjects or Others** – This is a regulatory phrase which requires reporting of this event to the IRB and to the government. 45 C.F.R. § 46.103(d)(5); 21 C.F.R. § 56.108(b)].

**Voluntary** – Free of coercion, duress, or undue influence.

**Vulnerable population** – This is a regulatory phrase which refers to a group of people who have some condition or situation that makes them more susceptible to coercion or undue influence. 45 C.F.R. § 46.107(a).

**Waiver of Informed Consent** – An action taken by the IRB permitting the investigator to pursue research involving human subjects without obtaining informed consent. 45 C.F.R. 46.116(d).

## Appendix B – TERMS OF FEDERALWIDE ASSURANCE

# FEDERALWIDE ASSURANCE (FWA) FOR THE PROTECTION OF HUMAN SUBJECTS

**U. S. Department of Health and Human Services (HHS)**
**Office for Human Research Protections (OHRP)**

### A. TERMS OF THE FEDERALWIDE ASSURANCE (FWA) FOR INSTITUTIONS WITHIN THE UNITED STATES

#### 1. Human Subjects Research Must be Guided by Ethical Principles

All of the Institution's human subjects research activities, regardless of whether the research is subject to federal regulations, will be guided by the ethical principles in: (a) The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, or (b) other appropriate ethical standards recognized by federal departments and agencies that have adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule.

#### 2. Applicability

These terms apply whenever the Institution becomes engaged in human subjects research conducted or supported* by any federal department or agency that has adopted the Common Rule, unless the research is otherwise exempt from the requirements of the Common Rule or a department or agency conducting or supporting the research determines that the research shall be conducted under a separate assurance. In general, the Institution becomes so engaged whenever (a) the Institution's employees or agents intervene or interact with human subjects for purposes of federally-conducted or –supported research; (b) the Institution's employees or agents obtain individually identifiable private information about human subjects for purposes of federally-conducted or –supported research; or (c) the Institution receives a direct federal award to conduct human subjects research, even where all activities involving human subjects are carried out by a subcontractor or collaborator.

[*Federally-supported is defined throughout the FWA and the Terms of Assurance as the U.S. Government providing any funding or other support.]

#### 3. Compliance with the Federal Policy for the Protection of Human Subjects and Other Applicable Federal, State, Local, or Institutional Laws, Regulations, and Policies

When the Institution becomes engaged in federally-conducted or -supported human subjects research to which the FWA applies, the Institution and the institutional review boards (IRBs) designated under the Institution's Assurance will comply with the Federal Policy for the Protection of Human Subjects.

The reference in the Code of Federal Regulations is shown below for each department and agency which has adopted the Common Rule:

| | |
|---|---|
| 7 C.F.R. part 1c | Department of Agriculture |
| 10 C.F.R. part 745 | Department of Energy |
| 14 C.F.R. part1230 | National Aeronautics and Space Administration |
| 15 C.F.R. part 27 | Department of Commerce |
| 16 C.F.R. part 1028 | Consumer Product Safety Commission |
| 22 C.F.R. part 225 | Agency for International Development |
| 24 C.F.R. part 60 | Department of Housing and Urban Development |
| 28 C.F.R. part 46 | Department of Justice |
| 32 C.F.R. part 219 | Department of Defense |
| 34 C.F.R. part 97 | Department of Education |
| 38 C.F.R. part 16 | Department of Veterans Affairs |
| 40 C.F.R. part 26 | Environmental Protection Agency |
| 45 C.F.R. part 46 | Department of Health and Human Services |
| 45 C.F.R. part 46 | Central Intelligence Agency (by Executive Order 12333) |
| 45 C.F.R. part 690 | National Science Foundation |
| 49 C.F.R. part 11 | Department of Transportation |

For any federally-conducted or -supported human subjects research to which the FWA applies, the Institution also will comply with any additional human subjects regulations and policies of the department or agency which conducts or supports the research and any other applicable federal, state, local, or institutional laws, regulations, and policies. When the Institution is engaged in human subjects research conducted or supported by the Department of Health and Human Services (HHS), the Institution will comply with all subparts of the HHS regulations at Title 45 Code of Federal Regulations part 46 (45 C.F.R. part 46, subparts A, B, C, and D).

Human subjects research conducted or supported by each federal department or agency listed above will be governed by the regulations as implemented by the respective department or agency. The head of the department or agency retains final judgment as to whether a particular activity conducted or supported by the respective department or agency is covered by the Common Rule. If the Institution needs guidance regarding implementation of the Common Rule and other applicable federal regulations, the Institution should contact appropriate officials at the department or agency conducting or supporting the research. For federally-conducted or –supported research covered by the FWA, the department or agency that conducts or supports the research retains final authority for determining whether the Institution complies with the Terms of Assurance. If HHS receives an allegation or indication of noncompliance related to human subjects research that is covered by the FWA and is conducted or supported solely by a Common Rule department or

agency other than HHS, HHS will refer the matter to the other department or agency for review and action as appropriate.

Please note that if the Institution voluntarily extends the Common Rule or the Common Rule and subparts B, C, and D of the HHS regulations at 45 C.F.R. part 46 to all research regardless of support, OHRP will have the authority to ensure that the Institution complies with this commitment for all research to which the FWA applies that is not federally-conducted or –supported.

**4. Written Procedures***

a) The Institution submitting the FWA has written procedures* for ensuring prompt reporting to the IRB, appropriate institutional officials, the head of any department or agency conducting or supporting the research (or designee), any applicable regulatory body, and OHRP of any:

1. unanticipated problems involving risks to subjects or others;

2. serious or continuing noncompliance with the federal regulations or the requirements or determinations of the IRB(s); and

3. suspension or termination of IRB approval.

Upon request, the Institution will provide a copy of these written procedures to OHRP and any department or agency conducting or supporting research covered by the FWA.

b) The Institution must ensure that the IRB(s) designated under the FWA has established written procedures* for:

4. conducting IRB initial and continuing review (not less than once per year) of research, and reporting IRB findings to the investigator and the Institution;

5. determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review; and

6. ensuring prompt reporting to the IRB of proposed changes in a research activity and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects.

Upon request, the Institution will provide a copy of these written procedures to OHRP and any department or agency conducting or supporting research covered by the FWA.

[*For HHS-conducted or -supported human subjects research, see OHRP guidance on written IRB procedures on the OHRP website at http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd702.htm ]

**5. Scope of IRB(s)'s Responsibilities**

All human subjects research to which the FWA applies, except for research exempted or waived in accordance with Sections 101(b) or 101(i) of the Common Rule, will be reviewed, prospectively

approved, and subject to continuing review at least annually by the designated IRB(s). The IRB(s) will have authority to approve, require modifications in, or disapprove the covered human subjects research. For research approved by the IRB(s), further appropriate review and approval by any department or agency conducting or supporting the research or by officials of the institution holding the FWA may be required.

**6. Informed Consent Requirements**

Except for research exempted or waived in accordance with Sections 101(b) or 101(i) of the Common Rule, informed consent for research to which the FWA applies will be:

a) sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, Section 116 of the Common Rule; and

b) appropriately documented, in accordance with, and to the extent required by, Section 117 of the Common Rule.

**7. Requirement for Assurances for Collaborating Institutions**

When the Institution holding the FWA is either a) the primary awardee under a federal grant, contract, or cooperative agreement supporting research to which the FWA applies, or b) the coordinating center for federally-conducted or –supported research to which the FWA applies, the Institution is responsible for ensuring that all collaborating institutions engaged in such research operate under an appropriate OHRP-approved or other federally-approved assurance for the protection of human subjects.

An institution holding an FWA may collaborate with another institution that does not have an FWA. In such circumstances, a collaborating institution may operate under the FWA with the approval of the department or agency conducting or supporting the research and the institution holding the FWA.

For federally-conducted or –supported research covered by the FWA, the department or agency that conducts or supports the research retains final authority for determining which institutions are engaged in the research and need to hold an assurance for the protection of human subjects.

**8. Written Agreements with Independent Investigators Who are not Otherwise Affiliated with the Institution**

When the Institution holding the FWA is either a) the primary awardee under a federal grant, contract, or cooperative agreement supporting research to which the FWA applies, or b) the coordinating center for federally-conducted or –supported research to which the FWA applies, the Institution is responsible for ensuring that all collaborating independent investigators engaged in such research operate under an appropriate OHRP-approved or other federally-approved assurance for the protection of human subjects.

The engagement in federally-conducted or –supported human subjects research activities to which the FWA applies by each independent investigator who is not otherwise an employee or agent of the Institution may be covered under the FWA only in accordance with a formal, written agreement of commitment to relevant human subject protection policies and IRB review. OHRP's

sample Individual Investigator Agreement (see http://www.hhs.gov/ohrp/humansubjects/assurance/unaflsup.rtf) may be used or adapted for this purpose, or the Institution may develop its own commitment agreement in coordination with the department or agency conducting or supporting the research. Institutions must maintain commitment agreements on file and provide copies upon request to OHRP and any department or agency conducting or supporting the research.

For federally-conducted or –supported research covered by the FWA, the department or agency that conducts or supports the research retains final authority for determining which independent investigators are engaged in the research and need to be covered by a written commitment agreement with the institution holding the FWA.

**9. Institutional Support for the IRB(s)**

The Institution will ensure that each IRB designated under the FWA has meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

**10. Compliance with the Terms of Assurance**

The Institution accepts and will follow items 1-9 above and is responsible for ensuring that (a) the IRB(s) designated under the FWA agree to comply with these terms; and (b) the IRB(s) possess appropriate knowledge of the local research context for all research to which the FWA applies (please refer to the OHRP Guidance on IRB Knowledge of Local Research Context on the OHRP website at http://www.hhs.gov/ohrp/humansubjects/guidance/local.htm).

Any designation under the FWA of the IRB of another institution or organization must be documented by a written agreement between the Institution holding the FWA and the IRB organization outlining their relationship and include a commitment that the designated IRB will adhere to the requirements of the FWA. OHRP's sample IRB Authorization Agreement may be used for such purpose, or the parties involved may develop their own agreement. This agreement should be kept on file at both institutions/organizations and made available upon request to OHRP and any department or agency conducting or supporting research covered by the FWA.

**11. Assurance Training**

The OHRP Assurance Training Modules (see http://137.187.172.153/CBTs/Assurance/login.asp) describe the major responsibilities of the Institutional Signatory Official, the Human Protection Administrator (e.g., Human Subjects Administrator or Human Subjects Contact Person), and the IRB Chair(s) that must be fulfilled under the FWA. OHRP strongly recommends that the Institutional Signatory Official, the Human Protections Administrator, and the IRB Chair(s) personally complete the relevant OHRP Assurance Training Modules, or comparable training that includes the content of these modules, prior to submitting the FWA.

**12. Educational Training**

OHRP strongly recommends that the Institution and the designated IRB(s) establish educational training and oversight mechanisms (appropriate to the nature and volume of its research) to ensure that research investigators, IRB members and staff, and other appropriate personnel maintain continuing knowledge of, and comply with, the following: relevant ethical principles; relevant

federal regulations; written IRB procedures; OHRP guidance; other applicable guidance, state and local laws; and institutional policies for the protection of human subjects. Furthermore, OHRP recommends that a) IRB members and staff complete relevant educational training before reviewing human subjects research; and b) research investigators complete appropriate institutional educational training before conducting human subjects research.

**13. Renewal of Assurance**

All information provided under the FWA must be renewed or updated at least every 36 months (3 years), even if no changes have occurred, in order to maintain an active FWA. Failure to update this information may result in restriction, suspension, or termination of the Institution's FWA for the protection of human subjects.

**DOMESTIC INSTITUTIONS ACCEPTING THESE TERMS MAY PROCEED WITH THE ASSURANCE FILING PROCESS**

# Appendix C – BELMONT REPORT

## The Belmont Report

### Ethical Principles and Guidelines for the Protection of Human Subjects of Research

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

### April 18, 1979

*Ethical Principles and Guidelines for Research Involving Human Subjects*

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

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

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

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

#### A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate

a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

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

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

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

**B. Basic Ethical Principles**

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

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

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

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

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

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

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

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

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

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

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

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

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

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability,