

***INSTITUTIONAL REVIEW BOARD  
(IRB)  
AT  
CALIFORNIA PACIFIC  
MEDICAL CENTER***

**GUIDELINES FOR  
RESEARCH INVOLVING  
HUMAN SUBJECTS**

**Assurance Number: FWA00000921**

*California Pacific  
Medical Center*

*The Smith-Kettlewell  
Eye Research Institute*

*University of the Pacific  
School of Dentistry*

## References [Links]

The Belmont Report

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm>.

NIH-OHRP "Frequently Asked Questions"

<http://ohrp.osophs.dhhs.gov/index.htm>

NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>

Additional DHHS Protections for Children (45 CFR46.401-409)

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm#subpartd>

Research Involving Individuals with Questionable Capacity to Consent

<http://www.nih.gov:80/grants/policy/questionablecapacity.htm>

Food and Drug Administration Information Sheets (includes Frequently Asked Questions)

<http://www.fda.gov/oc/ohrt/irbs/default.htm>

NIH Website for Clinical Trials

<http://www.clinicaltrials.gov/ct/info/resources>

## SECTION 1

### INTRODUCTION

These guidelines have been written to assist an investigator in developing protocols and submitting them for approval by the California Pacific Medical Center (CPMC) Institutional Review Board (IRB).

Before a research project involving human subjects is initiated, it must be reviewed and approved by the Institutional Review Board (IRB). While the principal investigator has primary responsibility for the conduct of the study, the CPMC IRB is responsible for protecting the rights and welfare of research subjects. Through its Federalwide Assurance, the CPMC IRB is held accountable to federal agencies that have established guidelines for the use of human subjects in research.

The CPMC IRB is located at 2200 Webster Street, 5<sup>th</sup> Floor, PACIFIC Campus.

#### **A. Other Administrative Offices for Researchers**

In addition to the IRB review process, all human research with external support (funds, drugs, or devices) must be processed through one of two other administrative offices, depending on the source of support: (1) the Office of Clinical Research provides institutional support for industry sponsored projects, including negotiation of contracts if applicable; and (2) the Office of Research Finance provides institutional sign-off for projects conducted by the research institute's investigators with government, foundations, or private support. Both offices establish research accounts.

#### **B. Federalwide Assurance**

The CPMC IRB has filed an assurance of compliance, called a Federalwide Assurance, with the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (DHHS). The CPMC IRB is required to enter into this agreement because it receives federal funding for research involving human subjects.

A Federalwide Assurance (FWA) is a binding written agreement between the CPMC IRB and DHHS. It states that this IRB is guided by the ethical principles of the Belmont Report, and will comply with federal regulations (45 Code of Federal Regulations Part 46, or simply 45 CFR 46) for all federally funded human subjects research.

The federal regulations of 45 CFR 46 require the establishment of an Institutional Review Board to review and approve human subjects research prior to its initiation. These regulations also require that specific points of information be included in the informed consent process, and that, in most cases, the consent process itself be documented in writing.

California Pacific Medical Center (CPMC), University of the Pacific School of Dentistry (UOP), and The Smith Kettlewell Eye Research Institute (SKERI) have its own FWA. CPMC IRB provides IRB review for human subjects research conducted at CPMC (Pacific, California, and Davies Campuses), UOP, and SKERI under a DHHS Authorization Agreement. Projects reviewed from UOP and SKERI receive the same IRB review as those conducted at CPMC.

The Federalwide Assurance describes the responsibilities of the institution, the Institutional Review Board, and the investigators. All investigators are expected to conduct research in accordance with the provisions of the Federalwide Assurance. Primary responsibility for assuring that the rights and welfare of the individuals involved are protected rests with principal investigator conducting the research. Principal investigators who assign or supervise research conducted by co-investigators (ex. study coordinators, research fellows) have an obligation to consider carefully whether they are qualified to safeguard adequately the rights and welfare of subjects.

A copy of the FWA document is available upon request from the IRB staff.

### **C. Mandate of Committee**

The IRB's primary responsibility is the protection of subjects from undue risk and from deprivation of personal rights and dignity. This protection is best assured by the following considerations:

1. That there is *voluntary participation* by the subjects, indicated by free and *informed consent* and
2. That an appropriate *balance* exists between potential *benefits* of the research to the subject or to society and the *risks* assumed by the subject.

The IRB fulfills its mandate by reviewing all protocols submitted to it for scientific merit and ethical considerations prior to approval. By doing so, the IRB oversees the protection of volunteers' welfare, dignity and privacy. These elements of protection are meant to ensure that the legitimate impulse for knowledge is kept in integral relation with other human values. Thus, the design of the study must be sound, and the nature and likelihood of all **risks** and **benefits** must be made clear in all protocol applications to the IRB.

This institution assures that before human subjects are involved in non-exempt research, the IRB will give proper consideration to:

1. the risks to the subjects,
2. the anticipated benefits to the subjects and others,
3. the importance of the knowledge that may reasonably be expected to result, and
4. the informed consent process to be employed.

Risks to research subjects posed by participation in research should be justified by the anticipated benefits to the subjects or society. This requirement is clearly stated in all codes of research ethics, and is central to the federal regulations. One of the major responsibilities of the IRB, therefore, is to assess the risk and benefits of proposed research.

#### **D. Definitions**

- **Benefit:** A valued or desired outcome; an advantage.
- **Minimal Risk:** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (Federal Policy 46.102(i)). For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination. The definition of minimal risk for research involving prisoners differs somewhat from that given for noninstitutionalized adults.
- **Risks:** The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only "minimal risk".

#### **E. Considerations**

The IRB's assessment of risks and anticipated benefits involves a series of steps. The IRB must:

1. identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research;
  2. determine that the risks will be minimized to the extent possible;
  3. identify the probable benefits to be derived from the research;
  4. determine that the risks are reasonable in relation to benefits to subjects, if any, and the importance of the knowledge to be gained;
  5. assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits; and
  6. determine intervals of periodic review, and where appropriate, determine that adequate provisions are in place for monitoring the data collected.
- **Identification and Assessment of Risks.** In the process of determining what constitutes a risk, only those risks that may result from the research, as distinguished from those associated with therapies subjects would undergo even if not participating in research, should be considered.
  - **Physical Harm.** Medical research often involves exposure to minor pain, discomfort, or injury from invasive medical procedures, or harm from possible side effects of drugs. All of these would be considered "risks" for purposes of IRB review.
  - **Psychological Harm.** Participation in research may result in undesired changes in thought processes and emotion (e.g., episodes of depression, confusion, or hallucination resulting from drugs, feelings of stress, guilt, and loss of self-esteem). These changes may be transitory, recurrent, or permanent.
  - **Social and Economic Harm.** Some invasions of privacy and breaches of confidentiality may result in embarrassment within one's business or social group, loss of employment, or criminal prosecution. Participation in research may result in additional actual costs to individuals. Any anticipated costs to research participants should be described to prospective subjects during the consent process.

- **Assessment of Anticipated Benefits.** The benefits of research fall into two major categories: benefits to subjects and benefits to society. Frequently, the research subjects are undergoing treatment, diagnosis, or examination for an illness or abnormal condition. This kind of research often involves evaluation of a procedure that may benefit the subjects by ameliorating their conditions or providing a better understanding of their disorders. Patients and healthy individuals may also agree to participate in research that is either not related to any illnesses they might have or that is related to their conditions but not designed to provide any diagnostic or therapeutic benefit. Such research is designed principally to increase our understanding and store of knowledge about human physiology and behavior. Research that has no immediate therapeutic intent may, nonetheless, benefit society as a whole. These benefits take the form of increased knowledge, improved safety, technological advances, and better health. The IRB assures that the anticipated benefits to research subjects and the knowledge researchers expect to gain are clearly identified.

Direct payments or other forms of remuneration offered to potential subjects as an incentive or reward for participation should not be considered a "benefit" to be gained from research. Although participation in research may be a personally rewarding activity or a humanitarian contribution, these subjective benefits do not enter into the IRB's analysis of benefits and risks.

#### **F. Conflict of Interest**

A conflict of interest is a situation where an investigator's outside financial interest(s) or obligation(s) bias or have the potential to bias a research project. Federal regulations require disclosure and management of actual or apparent conflicts of interests.

Investigators conducting research funded by the Public Health Service (including National Institutes of Health) and National Science Foundation, as well as those conducting studies regulated by the Food and Drug Administration, are subject to agency specific regulations. These regulations set forth the obligations of investigators, sponsors and institutions for research involving significant financial or other conflicts of interest, and affected parties are advised to review the relevant regulations prior to submissions of a research proposal or application.

The Conflict of Interest (COI) Committee is chaired by the Scientific Director of CPMC Research Institute. The COI Committee is made up of lay members, doctors, and research institute personnel.

The COI Committee reviews cases in which an investigator has disclosed significant financial interests that may be affected by the results of his/her research project and recommends management strategies to CPMC IRB. Management strategies are developed and implemented to address conflicts of interest and to assure that the investigator may satisfy his/her research obligations in an objective manner and to avoid and/or mitigate concerns of bias. Management strategies that may be considered in addressing conflicts range from no action required other than disclosure, to that of disqualification of the investigator from participating in the project, as well as others.

Release of the study by CPMC IRB is contingent upon IRB receipt and review of the management strategy. The strategy recommended by the COI Committee and the IRB must be accepted and will be implemented by the principal investigator before final approval is granted by the IRB.

## G. At CPMC, whose research must be reviewed?

The federal regulations define “RESEARCH” as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research even if they are a component of a larger non-research activity (e.g., instruction, demonstration).

An established and accepted diagnostic or therapeutic procedure done for the benefit of a patient is not an experiment and hence not within the IRB jurisdiction to review, unless it is done as part of a comparison of standard practices. Risks of any innovation applied to a patient for the sole purpose of aiding that individual are governed by the customary ethics of medicine and do not require IRB review. On the other hand, when innovative diagnostic or therapeutic procedures are considered part of a study, they must be reviewed by the IRB in accordance with the regulations. For example, a research study is by definition undertaken if, in addition to patient care, information is gathered for scientific purposes, or if it is contemplated that innovative treatment on one patient will be repeated in the same (or other) patient(s) in order to compare it to standard treatment.

As required under CFR 46.119, “Research Undertaken Without the Intention of Involving Human Subjects”, in the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by the IRB.

When innovative diagnosis or therapy of one patient involves emergency use of an investigational new drug or device, the physician must follow the FDA regulations which allow one-time use at an institution of an investigational drug or device for emergency purposes, and require reporting this use within 5 working days to the IRB.

Research investigators are responsible for ensuring that all research involving human subjects is submitted to the IRB *prior to implementation*. Failure to obtain approval in advance, carrying out the project after disapproval, or failure to comply with DHHS/Assurance guidelines is unlawful and unethical; it will result in no legal protection nor assistance by the investigator's institution.

The use of any investigational drug or device which has not yet been approved by the Food and Drug Administration (FDA) constitutes research and must be approved by the IRB.

Research plans that propose the use of living human subjects, tissues, or materials from living humans or data on humans must be reviewed and approved by the IRB *before the research begins*. This includes research that is:

1. sponsored by this institution, or
2. conducted by or under the direction of any employee or agent of this institution in connection with his or her institutional responsibilities, or
3. conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution, or
4. using this institution's non-public information to identify or contact human research subjects or prospective subjects.

## **H. For proposals involving new (off-label) use of an FDA approved drug or device**

Good medical practice requires that physicians use legally available drugs, biologics, and devices according to their best knowledge and judgment. If a physician intends to use a product for an indication that is not included in the approved labeling for that product, she/he has 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. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an IRB.

If, however, a physician wishes to study the effects of an approved drug or medical device and devises a research protocol to collect data for studying the effects of the drug or device, then the physician must apply for an IRB approval.

The physician should contact the IRB for further guidance or may contact the FDA directly (see contact information below).

*For drugs, call 301-827-4573 to obtain information regarding:*

- the legal status of a test article (e.g., whether an article is a "drug," or whether a drug is approved for marketing);
- whether research with a marketed drug in a particular study "significantly increases the risks" (or decreases the acceptability of the risks) and therefore requires an IND; and
- whether an investigational new drug application (IND) is required for a drug study.

*For medical devices, call 301-594-1190 to obtain information regarding:*

- whether an investigational device exemption (IDE) is required for a device study; and
- whether a device is deemed "significant risk" or "non-significant risk";

## **I. The Definition of Human Subject**

The federal regulations define a human subject as a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. Intervention includes both physical procedures by which data are gathered (e.g., drawing blood) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., medical record information). Since the definition of a human subject is a "living" individual, research involving autopsy materials or cadavers is not considered human subjects research and is not reviewed by the IRB.

## **J. Participation by the Principal Investigator**

The Principal Investigator bears the ultimate responsibility for the conduct of a research project. Following are the investigator's list of responsibilities:

1. The investigator in charge of the project may request to and/or may be requested by the IRB to present his/her research proposal and to answer any questions that might arise regarding his/her protocol. New principal investigators are encouraged to attend and meet with the IRB to briefly discuss his/her research protocol. The investigator will be notified by the IRB staff prior to the IRB meeting at which the protocol is to be reviewed.
2. The principal investigator acknowledges and accepts his/her responsibility for protecting the rights and welfare of human research subjects.
3. The principal investigator who intends to involve human research subjects will not make the final determination of exemption from applicable federal regulations or provisions of the CPMC IRB Assurance. (This is made by the IRB Chair.)
4. The principal investigator is responsible for keeping a copy of the IRB-approved and subject signed informed consent document in each patient's study file unless the IRB has specifically waived this requirement. A signed copy is to be given to the patient and the original placed in the subject's medical record.
5. The principal investigator will promptly report proposed changes in previously approved human subject research activities to the IRB. The proposed changes will not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.
6. The principal investigator is responsible for reporting progress of approved research to the **IRB at least once a year** on the basis of risks to subjects.
7. The principal investigator will forward certification of IRB approval of proposed research to the appropriate Federal Department or agency.
8. The principal investigator will report promptly to the IRB, appropriate institutional officials, the Office of Human Research Protections (OHRP), sponsor, and/or any other sponsoring Federal department or agency head, as appropriate, any injuries to human subjects or any other unanticipated problems involving significant risks to subjects or others.

## **K. Application Deadlines**

The IRB meets twice each month. A calendar of the meeting dates and submission deadlines is available on the CPMC IRB website. All submissions must be in the IRB Administrative Office by 3:00 p.m. on the submission due date listed on the calendar.

## SECTION 2

### TYPES OF SUBMISSIONS

#### **A. The following are the types of submissions for IRB review:**

##### **1. Initial Submissions**

- Full Board Review [more than minimal risk study]
- Expedited Review [no more than minimal risk study]
- Exempt Status Review

##### **2. Protocol Amendments/Modifications**

##### **3. Research –related Documents**

- Recruitment Materials
- Correspondence
- Brochures (e.g. Investigator’s Brochure)

##### **4. Unanticipated Risks or Serious Adverse Events (SAE) Reports/IND Safety Reports [prompt reporting required for on site events (CPMC subjects)]**

##### **5. Progress Report**

- Annual/Continuing Review reports (or as requested)

The IRB staff will receive from investigators all research protocols which involve human subjects. The IRB staff is responsible for the administrative processing and returning all disapproved protocols to investigators. In addition, the IRB staff will provide courtesy notice to approved investigators regarding the impending expiration of IRB approval and will maintain a database of all studies.

Upon receipt of new protocols, scientific merit reviews are conducted on all studies, except those qualifying as exempt. These evaluations are provided along with the study protocol for all IRB members to review. The studies are discussed at the next scheduled IRB meeting. The investigator's attendance at that meeting is optional. He/she may request to and/or may be requested by the IRB to present his/her research proposal and to answer any questions that might arise regarding his/her protocol. The investigator will be notified by the IRB staff prior to the IRB meeting at which the protocol is to be reviewed.

IRB decisions and requirements for modifications will be conveyed to investigators in writing, **seven working days after the IRB meeting**. Written notification of decisions to disapprove will be accompanied by reasons for the decision with provision of an opportunity for reply by the investigator, in person or in writing.

Once a protocol has been approved for scientific merit and all questions and concerns have been addressed satisfactorily by the investigator, the IRB may vote to **fully approve** the study (approved as submitted). The IRB approval of any project is for a maximum of one year; or earlier review may be stipulated by the IRB.

The IRB may vote to give **conditional approval** (also known as “approved pending”) pending receipt of scientific merit review if they have not been completed by the meeting. “Approved pending” is usually approval contingent on specific changes to the consent form or protocol. The investigator makes changes requested by the IRB and submits the revised consent form or protocol to the IRB office for final review and approval by the IRB Chair. However, the IRB Chair may elect to return revised protocols or consent forms to the full IRB for final decisions. The committee is informed at the next scheduled meeting of these approvals.

If a study is **disapproved** by a reviewer for scientific merit, the investigator should respond to specific comments in writing. The IRB and scientific merit reviewer will review the responses raised in an expeditious manner (usually 10 working days) and the investigator will be notified of the IRB decision at its next meeting.

The IRB may vote to **table** a study pending further clarifications or major consent form changes. The investigator responds in writing to the questions, making revisions where needed, and submits the original plus the appropriate number of copies of the revised protocol and consent form for full committee re-review at its next scheduled meeting.

## **B. Categories of Review**

Research projects are reviewed at a full board meeting unless the project can be classified as minimal risk and qualifies for exempt status or expedited review. **The type of review depends on the risks posed to potential subjects.**

According to the federal regulations, *minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.* Risk includes not only physical risk, but also psychological, emotional, legal, social, and financial. The definition of minimal risk serves as the starting point for the IRB chair's determination of the category of review. If a project meets the definition of minimal risk, and falls into an exempt or expedited category as described below, the chair alone (or his/her designee, an experienced member) may review and approve the project.

- **Exempt Research**

CPMC IRB policy requires that all human subjects research proposals be submitted for review. However, certain types of human subjects research may be classified as exempt from the federal regulations (45 CFR 46.101(b)). The IRB Chair (or his/her designee, an experienced member) is the sole authority for determining whether the research meets the exempt criteria. Exempt research projects generally have no requirement for continuing review; however the IRB Chair has the right to require continuing review with written justification to the principal investigator.

Exempt research is limited to research involving no more than minimal risk and the only involvement of human subjects is in one or more of the following categories. If the research falls into one of these categories but is determined to be more than minimal risk, it may not be classified as exempt:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special educational instructional strategies, or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, if: (a) information obtained is recorded in such a manner that human subjects cannot be identified, directly or through identifiers linked to the subjects; or (b) if subjects could be identified directly or through linked identifiers, disclosure of the human subjects' responses outside the research could not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. [NOTE: This category does not apply to studies involving minors with one exception -- the study is an observation of public behavior and the investigator does not participate in the activities being observed.]
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior not otherwise exempt under the above category, if: (a) the human subjects are elected or appointed public officials or candidates for public office; or (b) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, 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.
5. Research to evaluate or otherwise examine public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payments for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies if wholesome foods without additives are consumed; or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the EPA or the Food Safety and Inspection Service of the US Department of Agriculture.

- **Expedited Review**

Federal regulations recognize certain kinds of research that may be reviewed by an IRB through an expedited review procedure (45 CFR 46.110). **Expedited review DOES NOT MEAN “QUICK REVIEW”**. Expedited review means that the IRB Chair (or his/her designee, an experienced member) and the scientific merit reviewer are responsible for the review and approval.

The IRB Chair (or his/her designee, an experienced member) has the sole authority for determining whether the research meets the expedited criteria, based on risks posed to subjects. The IRB Chair retains the discretionary right to require full board review, even when the project appears to meet the criteria for expedited review.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless the investigator has documented that reasonable and appropriate protections that will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

Expedited review is limited to research involving no more than minimal risk and the only involvement of human subjects is in one or more of the following categories. **The activities listed are not deemed to be of minimal risk simply because they are included on the list.** Inclusion on the list merely means that the activity is eligible for expedited review when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. If the research project as a whole involves more than minimal risk, it must be reviewed by the full board even if the activities are limited to those listed.

1. Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.
2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows: (a) from healthy, nonpregnant adults, who weigh at least 110 pounds. For these subjects, amounts drawn may not exceed 550 ml in an 8 weeks period and no more than 2 times per week; or (b) from other adults and children, considering age, weight, and health, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and no more than 2 times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings, in a nondisfiguring manner; (b) deciduous teeth at the time of exfoliation; (c) permanent teeth if patient care indicates a need for extraction; (d) collection of excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) collection of both supra- and subgingival dental plaque and calculus, provided the collection procedure is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed they must be cleared/approved for marketing. Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, echography, ultrasound, infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight and health of the individual.
5. Research involving materials (data, documents, records or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
6. Collection of data from voice, video, digital or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.
8. Continuing review of research previously approved by the convened IRB where (1) the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; (2) where no subjects have been enrolled and no additional risks have been identified; or (3) where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

- **Full Board Review**

Human subjects research that is not classified as exempt or expedited requires review by the full IRB at a convened meeting. CPMC IRB meets bi-monthly (2<sup>nd</sup> and 4<sup>th</sup> Tuesday of the month). Applications are placed on a meeting's agenda in order of receipt in the IRB Office. Investigators are advised to allow a minimum of two weeks for an application to be scheduled for review at a convened meeting. Note that a full board meeting may be canceled by the IRB Chair due to inability to secure a quorum for the meeting and other reasons that may arise that will make a scheduled meeting unnecessary or otherwise inappropriate.

IRB members have 5 options to choose from when recording their determination:

1. Abstain from voting. There are only 2 reasons that an IRB member should abstain from voting: conflict of interest and insufficient information to make an informed determination.
2. Approved as submitted. The investigator is not required to make any changes in the protocol or consent document.
3. Conditionally approved or “approved pending”. This means that the protocol is approved if specific changes are to be made or if information is clarified as directed by the IRB. The IRB Chair is delegated with the responsibility of reviewing the response/s from the investigator. The final approval may be made in an expedited fashion by the IRB Chair.
4. Not approved or disapproved. When this determination is made, the IRB is not able to specify the conditions under which it would approve the protocol item at the time of the current meeting. The IRB letter will summarize the reasons that the committee was not able to approve the protocol.
5. Table. This determination is made when a protocol is still under evaluation by the IRB. The IRB letter will indicate the reasons for this determination and will include the information that the IRB needs to reconsider the study or the items to address if the investigator wishes to appeal the determination.

CPMC IRB uses the primary, secondary, and scientific merit reviewer system, in which the primary reviewer is the IRB chair and one IRB member is assigned the role of reviewing and presenting the study to the members at the full board meeting (secondary reviewer). The IRB invites scientific merit reviewers from within or outside CPMC, who have special expertise, to function as consultants to the IRB for a specific research proposal.

The three main reviewers of the protocol review the grant application itself (or the pharmaceutical protocol and Investigator's Brochure). The reviewers may contact the investigator for clarification prior to the meeting date. Any requests for revisions will come from the full board itself after the meeting.

At the discretion of the IRB chair and/or the secondary reviewer, the investigator may be invited to attend the meeting for the purpose of additional clarification or discussion. The investigator will be asked to leave the meeting for subsequent discussion and voting.

For continuing review applications, the IRB chair (as the primary reviewer) reviews the complete study specific file, which includes all modifications and reports of unanticipated problems involving risks to subjects.

The IRB chair leads the discussion of the new project or continuing review application during the meeting. The assigned secondary reviewer then presents the protocol to the members, i.e. project's purpose and design is discussed. The IRB considers the risks and potential benefits of the research. The IRB reviews the informed consent document to determine whether subjects are fully informed about the purpose of the study, the procedures involved, the risks, the benefits, and the fact that participation is voluntary. Advertisements and recruitment letters are also reviewed to ensure that they are not coercive or misleading.

In the event that the IRB chair has conflict of interest regarding a project under review, the IRB chair notifies the board in advance and the study is referred to another member for review to ensure that all criteria for approval of research have been fulfilled.

Selection of secondary reviewer and scientific merit reviewer are made by the IRB chair and/or IRB staff. Secondary reviewers are members of the IRB; scientific merit reviewers may or may not be IRB members. If necessary, more than one scientific merit reviewer may be requested to a protocol. Reviewers are requested to address study issues such as scientific design, ethical issues, potential risks or benefits, privacy and confidentiality concerns, or considerations relative to a particular study population.

No person with a conflict of interest may provide secondary or scientific merit review for a research protocol.

Secondary and scientific merit reviewers are provided a worksheet to ensure that all criteria for approval of research have been fulfilled. The completed scientific merit reviewer worksheet is distributed to all IRB members prior to the meeting.

The IRB may, at its discretion invite the scientific merit reviewer to attend the full board meeting during the review of a particular study.

Clarifications from the primary, secondary and scientific merit reviewers are forwarded to the investigator in writing; **seven working days** after the IRB meeting. Documentation of the discussion will be included in the meeting minutes.

### **C. Previously Approved Studies**

- **Protocol Amendments/Modifications**

Any change in the conduct of a study must be reviewed and approved by the IRB prior to implementing the change except when the change is necessary to eliminate apparent immediate hazards to subjects. Modifications include, but are not limited to, procedural changes to a protocol, adding or removing investigators, changing the title of the project, requesting additional subjects beyond the original approved number, new funding sources, new or revised advertisements, changes to informed consent documents, surveys, questionnaires, correspondence with potential or current subjects, or additional new items.

Minor modifications may be approved by the IRB Chair alone using the expedited review procedure. More extensive modifications may require full board review. In either case, revisions or clarifications may be required. Procedures for expedited or full board review, criteria for approval, and revision prior to approval, are identical to those described for new projects.

The IRB Chair decides if the amendment approval can be expedited or whether it needs to go forward for full IRB approval. This is based on the perceived level of risk to the research subjects.

Depending on complexity, the IRB Chair may request review of the amendment by one of the original scientific merit reviewers. If it is decided that the amendment and consent should receive full IRB review and approval, the committee reviews only the appropriate changes submitted in the consent rather than re-review the full consent (since it has already been approved).

The amendment should be in a format which can be appended to the approved protocol and be accompanied by a:

1. Cover letter explaining the nature of the proposed amendment;
2. Summary of protocol &/or consent changes
3. Revised protocol and/or revised consent form (clean and hi-lighted).

Once approved, a letter of approval is sent to the investigator with the expiration date unchanged.

- **Progress Reports/Continuing Review**

The IRB is required to review all non-exempt research projects at intervals appropriate to the degree of risk, but not less than once a year (45 CFR 46.109(e)). This is called "continuing review."

If a project initially received expedited review and risks to subjects remain minimal, the continuing review may be expedited (reviewed by the IRB Chair alone, generally within two weeks upon receipt).

If a project initially received full board review, the project generally requires full board continuing review.

Investigators are encouraged to allow two weeks for full board review and approval. A schedule for full board meetings is available on the IRB web site.

It is the principal investigator's responsibility to submit an application for continuing review allowing sufficient time to permit the IRB chair or full board to review and approve the application prior to its expiration date. As a courtesy to investigators, the IRB staff sends the principal investigator a fax reminder memo 15- 30 days before the project's expiration date (i.e., the due date for continuing review).

**NO HUMAN SUBJECTS ACTIVITY MAY TAKE PLACE AFTER THE EXPIRATION DATE** unless there is an over-riding safety concern and the investigator is actively pursuing approval. Continuing review information should be submitted on a progress report form. The progress report form is downloadable from the IRB website. Hard copies also are available from the IRB Office. Instructions for completing the form are self-contained. Applications must be typewritten or word-processed using the current version of the form.

The IRB expects the investigator to respond to all items on the application form. Incomplete applications may be returned to the investigator.

Procedures for expedited or full board review, criteria for approval, and revision prior to approval, are identical to those described above for new projects. Investigators are notified in writing within seven working days of the decision of the IRB and any changes required. Final approval is not granted until all required changes have been made and submitted for review and approval. Upon receipt of final approval, an approval letter signed by the IRB Chair is sent to the principal investigator. The approval letter indicates the type of review and the date of next continuing review. The letter reminds investigators that changes in research activity may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to subjects.

OHRP recommends that if the IRB does not re-approve a research project by the specified review date, subject accrual should be suspended pending re-review by the IRB. It is the policy of CPMC IRB that if an anniversary date passes and a progress report is not submitted, the study be **administratively closed**. Investigators will be notified of study closure by mail. Continuations of research interventions or interactions in subjects will be addressed on a case-by-case situations or instances that would seriously jeopardize the safety or well being of individual subjects. Investigators may re-submit an administratively closed protocol (following initial review requirements) for study continuation. Federal regulations do not allow grace period.

- **Unanticipated Risk/Serious Adverse Event Reports**

Investigators are required to report to the IRB any unanticipated problems that involve risk to research subjects or others.

Investigators are required to report to the IRB every LOCAL (involving CPMC subjects) serious adverse event (SAE) **within five working days**. These reports should include an opinion as to whether the event was or was not related to participation in the study and an opinion (with reasons specified) as to whether the event warrants a change in the protocol or the consent form.

Reports will be reviewed by the IRB Chair and on-site serious adverse events (events that involve CPMC, UOP, and SKERI subjects) will be reported to the full board at the next scheduled meeting. Action will be taken if the new information changes the risk/benefit evaluation or if the new information should be conveyed to currently enrolled subjects and should be included in a modified consent form. The IRB Chair shall have the authority to temporarily stop the study if there is a reasonable risk of a previously unanticipated harm to other subjects.

Notifications of adverse events which did not take place at CPMC sites (e.g. IND Safety Reports/Medwatch Reports) must be submitted to the IRB Office within 30 days of their receipt by the investigator. No response will be automatically sent to the investigator.

For studies that involve drugs or devices, the IRB uses the following definitions:

### **1. Serious Adverse Experience**

Any serious adverse experience (AE) *associated with the use of the drug/device* that results in any of the following outcomes: (1) death, (2) a life-threatening adverse experience, (3) inpatient hospitalization or prolongation of existing hospitalization, (4) a persistent or significant disability/incapacity, or (5) a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

## **2. Unexpected Adverse Event**

Any serious adverse experience *associated with the use of the drug/device/intervention*, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to subjects (in the informed consent document) and to the IRB.

- **Exceptions and Deviations in Approved Protocols**

In order to comply with: 21 CFR 56.108 (a) (3): “In order to fulfill the requirements of these regulations, each IRB shall... (a) follow written procedures: (3) for ensuring prompt reporting to the IRB changes in research activity....”, the IRB classifies violations into 2 categories:

**Exception:** A permission is granted by the sponsor to make an exception to the protocol to accommodate the needs of individual subjects.

**Deviation:** A protocol requirement is violated to accommodate an individual without seeking permission.

Any exception or deviation from the approved process must be reported to the IRB within five days of the event or of discovery of the event.

- **Noncompliance Investigations and Actions**

Information regarding noncompliance in human subjects studies may come to the attention of the IRB through several pathways. These include information contained in new applications, continuing reviews, adverse experience reports, and reports from collaborators, employees, or subjects.

The IRB Chair reviews allegations of noncompliance. The IRB Chair makes a determination as to whether the alleged practices appear to (1) cause injury or any other unanticipated problems involving risks to subjects or others, or (2) constitute serious or continuing noncompliance with IRB determinations or federal regulations. In such cases, the IRB Chair may suspend study procedures pending a timely investigation and review by the full IRB.

Investigations by the IRB focus on the protection of study subjects. In cases that involve allegations of research misconduct, the IRB Chair contacts the Scientific Director of the Research Institute for further action. This does not preclude the IRB Chair or any member of the IRB from independently contacting the institutional official about any allegation of scientific misconduct. Inquiries or investigations into research misconduct do not preclude IRB review and actions.

The following points outline recommended procedures for resolving alleged noncompliance:

1. When made aware of a potential problem, the IRB staff compiles file information and present concerns to the IRB Chair.
2. The IRB Chair makes a determination as to whether to pursue the matter with the Principal Investigator via telephone call, e-mail, paper memo, or in person. The purpose of such contact is fact-finding, i.e. to determine whether the problem is intentional, unintentional and/or the result of mistake or oversight.
3. The IRB Chair documents the outcome of any and all communications and discussions in writing, by either e-mail or paper memo with a copy to the IRB files. Such documentation should be factual and objective, and include timelines for resolution (e.g. meeting dates, response deadlines).
4. When the initial inquiry does not result in resolution of the matter, a meeting with the principal investigator is scheduled as soon as possible.
5. Any discussions and effort to achieve resolution are documented in the IRB files, and presented at the next IRB meeting by the IRB Chair.
6. When a review of relevant documents and meetings as described above does not lead to resolution, the IRB Chair schedules a review by the full IRB at the next available meeting.
7. If a quorum of IRB members are present, and after discussion, the IRB shall vote on recommended actions.
8. The IRB has the authority to suspend or terminate IRB approval of protocols that are found to be non-compliant with institutional policies and procedures, state laws, and/or federal laws or regulations. Other sanctions imposed by the IRB may include but are not limited to compliance audits, letters of reprimand, and restrictions on serving as an investigator on human subjects protocols.
9. The IRB sends written notification of actions taken to the principal investigator with copies to the Research Institute's Scientific Director, medical staff office and the investigator's department chair.

Following are examples of non-compliance:

1. Scientific Misconduct
  - Plagiarism, including misrepresentation of authorship or misappropriation of data
  - Fabrication, falsification or destruction of data
2. Serious or Continuing Regulatory Non-Compliance
  - Failure to obtain/maintain approval for research
  - Failure to obtain informed consent when required
  - Failure to file serious adverse event reports
  - Coercion of human subjects
  - Performance of an unapproved procedure
  - Performance of research at an unapproved site
  - Failure to file protocol modifications
  - Failure to adhere to an approved protocol
  - Any other failure to adhere to regulations, policies, procedures or special conditions related to research

## **Reporting to Federal Oversight Agencies**

The IRB Chair notifies the Research Institute's Scientific Director and they together notify OHRP (in accordance with the terms of the FWA) and the Food and Drug Administration (FDA) (for projects subject to 21 CFR Parts 50 and 56) in a timely manner of any:

- serious or continuing noncompliance;
- unanticipated problems involving risks to subjects or others; or
- suspension or termination of IRB approval for a project. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action.

- **Recruitment Materials/ Advertisements**

Advertisements for current IRB approved studies must be reviewed by the IRB prior to being used. The complete proposed text of the advertisements should be submitted and should include:

1. Clear presentation of participation in research.
2. Inclusion criteria (disease state, symptoms, etc.)
3. Product/project description.
4. Length of Study.
5. Contact person and number for information.
6. No misleading information ("FDA approved", "safe", etc.)
7. Location of the ad is also important information for the IRB.

The IRB follows the following guidelines from the FDA:

When advertising is to be used, the IRB reviews the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive and does not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol. The IRB also reviews the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB reviews the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The review of the final taped message prepared from IRB-approved text may be accomplished through expedited procedures. The IRB wishes to caution the clinical investigators to obtain IRB approval of message text prior to taping, in order to avoid re-taping because of inappropriate wording.

No claims should be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. Such representation would not only be misleading to subjects but would also be a violation of the Agency's regulations concerning the promotion of investigational drugs [21 CFR 312.7(a)] and of investigational devices [21 CFR 812.7(d)].

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" leads study subjects to believe they will be receiving newly improved products of proven worth. Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

- **Project Closure**

When a study ends, is closed, or canceled for any reason, a progress report form (available on the IRB web site) must be completed. The progress report form serves as notification to the IRB that continuing review of the study is no longer needed.

If no subjects have been enrolled in a study for a period of two or more years, the IRB may require that the project be re-submitted for IRB re-review or the project be closed, unless there are extenuating circumstances for keeping the project open (e.g., the study is about a rarely-seen condition).

A project that is closed to new subject enrollment may still be collecting follow-up data on subjects. In this case, the project must remain open and is subject to continuing review until all follow-up data collection has ceased. Once project closure in the progress report is noted, no more data may be collected about any of the subjects in that particular study.

If the investigator has not submitted a completed progress report by the continuing review date, the IRB sends a letter to the investigator, explaining that IRB approval has lapsed. It is the policy of CPMC IRB that if an anniversary date passes and a progress report is not submitted, the study will be administratively closed. Investigators will be notified of study closure by mail. Continuations of research interventions or interactions in subjects will be addressed on a case-by-case situations or instances that would seriously jeopardize the safety or well-being of individual subjects. Investigators may re-submit their protocol (following initial review requirements) for study continuation.

Submit to: *Research Coordinator,*  
*2200 Webster Street, 5<sup>th</sup> Floor, P-Campus,*  
*San Francisco, CA 94115*  
*(415) 600-3688 or (415) 600-3709*

Written correspondence from the IRB regarding the submission is sent in a timely fashion.

### IRB SUBMISSION REQUIREMENTS (checklist)

**FOR FULL COMMITTEE REVIEW** (new studies that involve more than minimal risk; use of new drugs, investigational devices, drug-sponsored studies; phase III studies, etc.)

A. Submit the original plus **25 copies** (**collated**, in the order listed) of the following:

- **IRB Full Committee Review Cover page with appropriate signatures**
- **Protocol Summary**
- **Investigator Initiated Protocol** (including bibliography, questionnaires, tests, survey instruments)
- **Recruitment documents** (advertisements, etc.)
- **Informed consent form** [Follow IRB Model Consent Forms: Biomedical, Behavioral or Blood Draws Only printed onto CPMC Form F-2611, if inpatient.]
- **HIPAA forms:** HIPAA Compliance Application Form and other applicable HIPAA documents--refer to HIPAA link on CPMC IRB website

B. Submit **3 copies** of the following (if applicable):

- **Sponsor's Protocol**
- **Investigators Brochure** (If this is unavailable submit a summary of the preclinical/animal data and any relevant clinical data (or grant application))

### **RESEARCH USING INVESTIGATIONAL DEVICES**

In accordance with the CPMC Sutter/CHS Policy Guidelines on accuracy in billing government programs and third party payers, it is mandatory that investigators notify CPMC's Research Institute when an investigational device is planned for use prior to submitting the study to the IRB. Complete the Device form to submit to the IRB with the protocol submission. Contact the IRB Coordinator at 600-3688 for further information.

Submit **3 copies** of the following (if applicable):

- Request for **Investigational Device Use** in a Patient Setting

**FOR EXPEDITED REVIEW** (refer to back of the expedited form for acceptable FEDERAL categories)

- **Complete the form with appropriate signatures.** Submit **two copies** of the Expedited Review form including supporting documents with a consent form following the appropriate model. Submissions qualifying for expedited review does not need full committee review but rather review by chair and one scientific merit review; internal review is usually completed within ten days of submission (no specific due date deadline).
- **Protocol Summary**
- **Informed consent form** [Follow IRB Model Consent Forms: Biomedical, Behavioral or Blood Draws Only printed onto CPMC Form F-2611, if inpatient.]
- **HIPAA forms:** HIPAA Compliance Application Form and other applicable HIPAA documents--refer to HIPAA link on CPMC IRB website

**FOR EXEMPT STATUS STUDIES** (refer to back of the exempt form for FEDERAL acceptable categories)

- **Complete form with appropriate signatures.** Submit **one copy** of the Exempt Status Review form including supporting documents. Submissions qualifying for exempt status do not need full committee review; internal review is usually completed within ten days of receipt (no specific due date deadline).
- **HIPAA forms:** HIPAA Compliance Application Form and other applicable HIPAA documents--refer to HIPAA link on CPMC IRB website.

## SECTION 3

### NEW PROJECT APPLICATIONS AND IRB REVIEW/APPROVAL

Investigators are required to submit an application for IRB review PRIOR to initiating a research project. The IRB cover page (full board, expedited or exempt) is downloadable from the IRB web site.

- **Signatures**

The principal investigator, in whose name a project is approved, must sign the IRB cover page assuring compliance with all federal, state, and institutional policies as they apply to the study.

The signature of the investigator's department chair also is required on the cover page.

A fellow may be listed as a co-investigator on the cover page. A CPMC medical staff must sign the application as the supervisor or the principal investigator. The medical staff's signature indicates that she/he has reviewed the application, that it is ready for IRB review, and that she/he assumes responsibility for oversight of the fellow's project.

- **Guidance**

The IRB expects the investigator to respond to all items on the IRB cover page. The most common problem with new applications is that not enough detail is provided for the IRB Chair or members to evaluate the study's purpose and/or procedures. In particular, investigators are encouraged to provide detailed information regarding how potential subjects are initially identified, and how consent is obtained. There is no such thing as providing too much detail when describing study procedures. The more complete the initial description is, the less likely that time will be spent with correspondence back and forth between the investigator and IRB staff and/or IRB Chair to fill in the details.

#### **Application Processing**

- **Screening**

All applications are screened by the IRB staff. If the application is missing signatures, incomplete, or otherwise not fully prepared for review, it may be returned to the investigator or additional information may be requested by phone or e-mail. Once a complete packet of information has been received, it is assigned an IRB number. IRB number remains with the study until the study is closed. The IRB number appears on all IRB correspondence regarding the study.

- **IRB Review**

The IRB Chair determines whether the project is eligible for exempt status, expedited review, or requires full board review. If exempt or expedited review is appropriate, the principal investigator will be notified in writing with requests for additional clarifications or documentation prior to final approval.

If the project requires full board review, the IRB staff notifies the investigator of the meeting date. The IRB staff distributes copies of the submission packets (cover page, protocol summary, consent documents, etc.) to members and reviewers about a week in advance.

The IRB Chair, secondary reviewer (IRB member), and the scientific merit reviewer (consultant) serve as the main reviewers of all protocols reviewed by the IRB. All reviewers review a complete packet which includes the application, consent document, and all supplemental materials (including, the complete protocol, investigator's brochure, study-related materials, questionnaires, advertisements, etc.).

All reviewers may contact the investigator in advance of the board meeting for additional information or clarification. Any requests for revisions will come from the full board itself after the meeting.

At the full board meeting, the project's purpose and design is discussed, and the IRB considers the risks and potential benefits of the research. The IRB reviews the consent document to determine whether subjects are fully informed about the purpose of the study, the procedures involved, the risks, the benefits, and the fact that participation is voluntary. Advertisements and recruitment letters are also reviewed to ensure that they are not coercive or misleading.

- **Criteria for Approval**

In order for the IRB (or IRB Chair in the case of expedited projects) to approve a project, the following requirements must be satisfied (45 CFR 46.111):

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117.
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

- **Revisions Prior to Final Approval**

For studies that are classified as exempt or expedited, the investigator must satisfactorily respond to all requests from the IRB Chair for revisions and or clarification. The IRB Chair may approve projects as submitted or require modifications prior to approval. The IRB Chair is not empowered to disapprove projects; in such cases, the application is submitted for full board review along with the comments and recommendations of the IRB Chair. When the IRB Chair determines the study is procedurally sound and all revisions have been made, she/he approves the project and determines the interval for the next continuing review. For studies that require full board review, the investigator receives a correspondence that describes the IRB's determinations. Studies may be:

1. Approved as submitted. The investigator is not required to make any changes in the protocol or consent document.
2. Conditionally approved or “approved pending”. This means that the protocol is approved if specific changes are to be made or if information is clarified as directed by the IRB. The IRB Chair is delegated with the responsibility of reviewing the response/s from the investigator. The final approval may be made in an expedited fashion by the IRB Chair.
3. Not approved or disapproved. When this determination is made, the IRB is not able to specify the conditions under which it would approve the protocol item at the time of the current meeting. The IRB letter will summarize the reasons that the committee was not able to approve the protocol
4. Table. This determination is made when a protocol is still under evaluation by the IRB. The IRB letter will indicate the reasons for this determination and will include the information that the IRB needs to reconsider the study or the items to address if the investigator wishes to appeal the determination.

- **Notification of Approval**

Once the IRB Chair has signed off on a project, only the principal investigator receives notification of approval via inter-campus or U.S. mail. It is the principal investigator's responsibility to maintain accurate files of IRB correspondence, approvals, and research records. The approval notification includes: IRB number, principal investigator's name, project title, approval date, review date, and type of application (new, continuing review, modification), and list of some investigator's responsibilities during the conduct of the study.

A copy of the consent document on which an IRB approval stamp has been stamped, usually in the lower right corner will be mailed as well. The approval stamp indicates the approval date. The investigator is **REQUIRED** to make copies of the original IRB-stamped documents for use with his/her research subjects.

In circumstances when the stamped document is not used, the document that is used must contain text that is identical to the stamped document.

- **Appeal of IRB Decisions**

The IRB may approve a research project pending specific required changes in procedures or in the consent document. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision.

In both cases, the investigator may appeal the decisions of the IRB **in writing**. The investigator should provide a rationale for the appeal and any other relevant supporting documentation.

At the discretion of the IRB Chair, the investigator may also make such an appeal in person to the IRB. The IRB will notify the investigator in writing of the discussion and vote on the appealed issue(s).

The Scientific Director of CPMC Research Institute has the authority to review decisions of the IRB. In the case of an approval decision, should the Scientific Director of CPMC Research Institute conclude that a project does not fully comply with policies or obligations of CPMC or the Research Institute, the project may be disapproved, suspended, or terminated on behalf of the institution. In the case of a decision by the CPMC IRB to disapprove, suspend, or terminate a project, the decision may not be reversed by the Scientific Director of CPMC Research Institute or any other officials of CPMC.

## SECTION 4

### CONSENT FORMS

One of the most important elements in any research involving human subjects is assurance of free and informed consent. There must be an understanding as completely as possible of what is to be done and what the potential risks and benefits are. The CPMC IRB attempts to assure free and informed consent of subjects through careful review of the recruitment and consent process as well as of the consent form or information sheet to be used with the subjects. Documentation of informed consent through use of a signed consent form (or unsigned information sheet as appropriate) is essential. The IRB fulfills its regulatory mandates by reviewing, requiring modifications in and ultimately approving consent form documents which serve as a reference tool explaining risks and benefits, etc.

The IRB has developed model consent forms for investigators to use as a format to follow when developing their study-specific consents. The samples are to be followed closely, using similar terminology as appropriate. The IRB not only reviews and approves consent forms, but also reviews the "process" for consent interviews in terms of how consent is obtained and by whom

The consent form should serve as a written summary of the exact information presented to prospective subjects before they agree to participate in the study. It is a useful reference for both the subject and the investigator, and should be stated in language comprehensible to the layperson (at a 7th or 8th grade level of understanding), making very clear the elective and volunteer nature of participation in the study.

Some common problems with the consent document include the use of jargon, technical, or scientific terms that a lay person would not understand, and units of measure given in metric rather than the lay equivalents. Ordinary language should replace technical terms (e.g., upper extremities are better referred to as arms, hematoma as a bruise, venipuncture as taking blood from your arm with a needle, and so forth.) But perhaps the most common problem with consent documents is that they are written at a reading level several grades higher than the average subject would understand. Consent documents should be written at a reading level that potential subjects would understand. For most projects, seventh grade reading level is suggested. Most word processing programs can determine a document's reading level.

CPMC IRB also requires the consent documents to be written in the SECOND PERSON format throughout.

Federal regulations stipulate basic required elements of informed consent. The IRB model consent form incorporates these regulations as well as state, institutional, and IRB requirements.

**All consent forms to be used with inpatients at CPMC need to be typed onto the CPMC Form #F-2611.**

Upon request, the IRB staff can review the consent form *prior to your copying it*. The investigator should allow time for this administrative review prior to submission deadline. Contact the staff office at (415) 600-3688 or (415) 600-3709 for an appointment.

## **1. The Standard Informed Consent Document**

The purpose of an informed consent document is to provide subjects with a written source of information for future reference and to document the fact that the process of informed consent occurred prior to the subject's participation. The form generally serves as a basis for the initial presentation of the study to the potential subject. Typically, informed consent is documented by using the written informed consent document approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the informed consent document should be given to the subject. Unless the investigator has requested a waiver of documentation of consent, the subject's signature on an informed consent document is required prior to beginning any study procedures.

The IRB expects all persons involved in obtaining informed consent to be individually listed as members of the research team.

The basic elements of informed consent, as described in 45 CFR 46.116, are as follows:

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others, which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
9. The federal regulations stipulate that additional elements of informed consent should be provided when appropriate. The additional elements include:
10. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.
11. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
12. Any additional costs to the subject that may result from participation in the research.
13. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
14. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
15. The approximate number of subjects involved in the study.

## **2. California's Additional Required Elements**

1. If a placebo is to be administered or dispensed to a portion of the subjects involved in a medical experiment, all subjects of such experiment shall be informed of that fact.
2. An estimate of the expected recovery time of the subject after the experiment.
3. The name, institutional affiliation, if any, and address of the person or persons actually performing and primarily responsible for the conduct of the experiment.
4. The name of the sponsor or funding source, if any, or manufacturer if the experiment involves a drug or device, and the organization, if any, under whose general aegis the experiment is being conducted.
5. The name, address, and phone number of an impartial third party not associated with the experiment, to whom the subject may address complaints about the experiment.
6. Subjects must sign and be given a copy of the Experimental Subject's Bill of Rights.

## **3. Consent Form Requirements**

The consent form must be:

- approved by the IRB
- signed by the subject or the subject's legally authorized representative (45 CFR 46.117 (a); FDA 21 CFR 50.27 (a); ICH 4.8.8)
- signed by the person who conducted the informed consent discussion (ICH 4.8.8)
- signed and dated copy must be given to the subject or legally authorized representative signing the form (45 CFR 46.117(a); FDA 21 CFR 50.27(a); ICH 4.8.11).

## **4. Assent Document**

The assent document is used when the investigator recruits subjects who, by age or circumstance, are not able to give legally effective informed consent. Minors by definition cannot give legal consent. When legally effective informed consent cannot be obtained, the investigator should obtain the "assent" of the minor. This form documents the minor's knowledgeable agreement, or assent, to participate in a research project. The investigator should respect the decision of a minor subject not to participate, even when the parent or authorized representative gives permission, unless specifically instructed otherwise by the IRB. For studies involving minors (those under 18 years of age), the IRB recommends that this form be used with the 7-12 age range, but it may also be used with teenagers to enhance their comprehension if the study involves complicated procedures. A template is available on the IRB web site.

Note: Exemption from committee review does not apply to research involving vulnerable populations or special classes of subjects. Contact the IRB Office for further information regarding research protocols involving minors.

## **5. Legal Property**

The consent forms are legally the property of the Institution (CPMC); however, subjects can request a copy of their own consent form. The researcher is responsible for maintaining consent forms for three years as prescribed by CPMC, the State of California, and the Federal government. According to California Administrative Code Title 22, medical records (where a copy of the consent forms are filed) are to be kept for 7 years following discharge for adults and for minors up to the age of 18 (or 19 years). CPMC retains all records for 19 years. The FDA requires retention up to three years after drug approval; and the NIH requires retention up to three years after closure of the study. The original signed consent form goes to CPMC Medical Records; copies should be kept in the investigator's study files.

## **6. Re-consenting**

When reviewing a consent document related to a continuing review of research, the IRB should ensure the following:

- Any significant new findings (e.g., risks or adverse events), which may relate to the subject's willingness to continue participation, must be provided to the subject.
- The current consent document should still be accurate and complete, which means that all elements required by federal regulations are included (e.g., see 45 CFR 46.116; 21 CFR 50.25)

If the change could affect the subject's willingness to participate, irrespective of whether it relates to an element of consent, the subject must be re-consented so that they may make an informed decision as to whether to continue participation.

If the change would not affect the subject's willingness to participate, but the change relates to an element of consent, re-consent may not be necessary. In such cases, it is at the IRB's discretion to either re-consent the subject or merely provide an informational sheet. For example, the IRB may decide not to re-consent study subjects (and merely provide an informational sheet) who have completed active participation or where the only change is the number of subjects in the study. However, in all borderline situations, it is recommended that the IRB err on the side of re-consenting. In all other circumstances, unless the IRB determines otherwise, the subject does not need to be informed of the change.

## **7. NIH Certificate of Confidentiality**

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect the privacy of research subjects by protecting investigators and institutions from being compelled to release information that could be used to identify subjects with a research project. Certificates of Confidentiality are issued to institutions or universities where the research is conducted. They allow the investigator and others who have access to research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

Identifying information is broadly defined as any item or combination of items in the research data that could lead directly or indirectly to the identification of a research subject.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring privacy to subjects.

Certificates can be used for biomedical, behavioral, clinical or other types of research that is sensitive. Sensitive means that disclosure of identifying information could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.

Examples of sensitive research activities include but are not limited to the following:

1. Collecting genetic information;
2. Collecting information on psychological well-being of subjects;
3. Collecting information on subjects' sexual attitudes, preferences or practices;
4. Collecting data on substance abuse or other illegal risk behaviors;
5. Studies where subjects may be involved in litigation related to exposures under study (e.g., breast implants, environmental or occupational exposures).

A Certificate of Confidentiality protects personally identifiable information about subjects in the research project while the Certificate is in effect. Generally, Certificates are effective on the date of issuance or upon commencement of the research project if that occurs after the date of issuance. The expiration date should correspond to the completion of the study. The Certificate will state the date upon which it becomes effective and the date upon which it expires. A Certificate of Confidentiality protects all information identifiable to any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate. However, the protection afforded by the Certificate is permanent. All personally identifiable information maintained about participants in the project while the Certificate is in effect is protected in perpetuity.

While Certificates protect against involuntary disclosure, investigators should note that research subjects might voluntarily disclose their research data or information. Subjects may disclose information to physicians or other third parties. They may also authorize in writing the investigator to release the information to insurers, employers, or other third parties. In such cases, researchers may not use the Certificate to refuse disclosure. Moreover, researchers are not prevented from the voluntary disclosure of matters such as child abuse, reportable communicable diseases, or subject's threatened violence to self or others. However, if the researcher intends to make any voluntary disclosures, the consent form must specify such disclosure.

In the informed consent document, investigators should tell research subjects that a Certificate is in effect. Subjects should be given a fair and clear explanation of the protection that it affords, including the limitations and exceptions noted above.

The investigator may choose to apply for a Certificate of Confidentiality on his or her own, or the IRB may require that an investigator obtain a Certificate prior to conducting the research. Complete information is available on the NIH Office of Extramural Research web site.

## **8. Safeguarding Confidentiality**

An issue of primary importance is the protection of confidentiality. The investigator must have sensible plans to protect the subject's identity as well as the confidentiality of the research records. Care should be taken to explain the mechanisms that have been devised, for example, the use of numbering or code systems or safely locked files in private offices. Furthermore, the investigator should describe who has access to the data and under what circumstances a code system may be broken.

Without appropriate safeguards, problems may arise from long-term retention of records. In special circumstances requiring additional safeguards to prevent potential criminal prosecution of the participating human subject, the IRB may require the destruction of all data that can identify the subjects.

Appropriate safeguards are required for situations of video or taped data and photographs since these media provide additional potential means for subject identification. Investigators must secure subject consent explicitly mentioning these practices. They should also explain plans for final disposition or destruction of such records.

## **9. Subject Compensation**

Payment for participation in research may not be offered to the subject as a means of coercive persuasion. Rather, it should be a form of recognition for the investment of the subject's time, loss of wages, or other inconvenience incurred. Accordingly, compensation may not be withheld contingent on the subject's completion of the study. In most cases involving continued participation, compensation should be given on a reasonable prorated basis to avoid the impression that the investigator is coercing the subject to continue in a study or is punishing the subject for non-compliance.

## **10. Non-English Speaking Subjects**

Research investigators may seek informed consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate. It is therefore critical that the information in the informed consent document be written in language that is understandable to the subject. The informed consent documents should be available in English and other languages as appropriate to the subject population. CPMC IRB requires that researchers develop foreign language consent documents when enrolling subjects whose native language is not English; as Federal regulations require the translation of consent forms into the language that is most easily understood by potential research subjects.

Consent forms should be available in English and other languages as appropriate to the subject population(s) anticipated for a particular research project. Development of non-English language consent forms will typically necessitate translation of the original consent from English to the second language and then back to English. Back translation is necessary to ensure that the information is correctly conveyed. "Back translation" is not required by the IRB; instead a certificate of accuracy from the translation agency should be submitted.

The CPMC IRB is required to review all English and non-English consent forms and recruitment tools. All versions of the consent forms should be submitted to the IRB along with a certification of accuracy for each translated document.

The following guidelines should only be used if a non-English speaking subject is *encountered unexpectedly*:

- An oral translation of a short form consent document that summarizes the elements of informed consent is to be provided to the subject.
- The research subject shall be provided with a short form consent document, written in the subject's native language that summarizes the basic elements of the informed.
- The research subject will be provided a written summary of what the protocol entails (the IRB-approved English language informed consent may serve as the summary).
- The witness should be fluent in both English and the language of the subject.

Copies of the short form consent documents, Experimental Subject's Bill of Rights, and HIPAA authorizations translated in Spanish & traditional Chinese are available at the IRB office.

Consent procedures:

- a. The standard (i.e. IRB approved) informed consent document should be presented verbally to the subject in his/her native language.
- b. With the agreement to participate in the research study:
  - The subject should sign and date the translated "short form" consent document.
  - The witness to the informed consent process shall sign and date the "short form" consent document and the protocol summary (IRB-approved English language informed consent form may serve as the summary). The interpreter may serve as the witness.
  - The person obtaining consent is to sign the summary.
- c. Copies of the signed "short form" consent document and the protocol summary (IRB-approved English language consent form may be used in place of the summary) shall be given to the subject with the originals of both documents retained in the investigator's research records.
- d. A statement in the research records should indicate that the translation took place; the name of the translator; and the translator's belief that the subject understands the study and the consent process.
- e. Family members as witness. Investigators should consider that in clinical consent, family members often shield their loved ones from bad news (i.e. risks of study). A proper medical translator is an important safeguard that should not be set aside lightly.

You may contact CPMC Interpreter Services for help with translating an IRB approved consent from English to needed language at (415) 600-0105. Additional investigator and IRB guidance from FDA and DHHS (OHRP) are available on the following links:

- Office of Human Research Protections Guidelines (OHRP):  
<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm>
- Food and Drug Administration (FDA):  
<http://www.fda.gov/oc/ohrt/irbs/informedconsent.html#nonenglish>

## **11. Consent for illiterate subjects**

Short form process is required and subject can mark their mark on the short form consent.

The Office for Human Research Protections (OHRP) considers the following procedure to be an acceptable option for satisfying the requirements of Department of Health and Human Services (HHS) regulations at 45 CFR 46.117(b)(1) for an illiterate subject or an illiterate legally authorized representative of a subject who lacks capacity to provide informed consent:

- A written consent document that embodies the elements of informed consent required under 45CFR46.116 is read to the subject or the subject's legally authorized representative by a member of the research team.
- An audiotape or videotape recording of the content of the written consent document is provided to the subject or the subject's legally authorized representative.
- Steps are taken to ensure that the subject or the subject's legally authorized representative has easy access to a tape recorder or VCR.
- The subject or the subject's legally authorized representative makes a mark on the informed consent document after having adequate opportunity to listen and/or watch the audiotape or videotape.

## **12. Consent for subjects with physical impairment**

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If:

(a) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (b) is able to indicate approval or disapproval to study entry; they may be entered into the study.

The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape or audio tape recording of the consent interview is recommended.

## **13. Waiver of Documentation of Consent**

In some situations, the IRB may waive the requirement for obtaining a signed informed consent document (45 CFR 46.117(c)). The regulations state that a signed consent form may be waived if the IRB determines that:

1. the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality; or [example: survey or interview studies that contain highly sensitive (e.g., criminal behavior, sexual behavior) questions.]
2. the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. [example: mail out surveys about topics that could not reasonably damage a participant's reputation or employability or be otherwise stigmatizing.]

Waiver of documentation of consent may mean that no written document is provided to the subject at all, for example, in a random-dial telephone survey study. In this type of study, the telephone interview would begin with a script that includes all of the required elements of consent, but the study subjects would receive no written information about the study, either before or after the interview. The telephone script containing the elements of consent must be submitted to the IRB prior to use.

On the other hand, the waiver of documentation of consent may mean only that the subject's signature does not have to be obtained. The regulations stipulate that the IRB chair may still require that the investigator provide the subject with a written statement about the research when granting a waiver of documentation. For example, in a mailed-out survey study, the chair may determine that it is reasonable for the investigator to provide the subjects with a cover letter containing all of the basic elements of consent. The letter would simply conclude with a statement that returning the survey or questionnaire would be considered agreement to participate.

#### **14. Waiver of Elements of Consent**

Some research projects would not be possible if informed consent from participants were required. The IRB may consider waiving the requirement for some or all of the elements of informed consent (45 CFR 46.116(d)). The regulations state that informed consent may be waived in full or in part if the IRB determines that:

1. the research involves no more than minimal risk to the subjects; and
2. the waiver or alteration will not adversely affect the rights and welfare of the subjects; and
3. the research could not practicably be carried out without the waiver or alteration; and
4. whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Examples of types of studies in which all of the elements of consent have been waived include retrospective chart reviews, or studies of existing pathology specimens (all specimens to be studied have already been collected and are "on the shelf" at the time of the IRB application). Presuming that the study can be classified as minimal risk and that adequate provisions for protecting the confidentiality of the data are in place, the IRB chair generally finds that obtaining not possible.

If an investigator does request a waiver of signed consent, then the application should provide a **written justification** for doing so and cite one of the above categories. As the federal regulations note, "in cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research".

#### **15. Experimental Subject's Bill of Rights**

For non-biomedical studies, the IRB may recommend use of the Experimental Subject's Bill of Rights, though it is not required by law. As an alternative, for studies which are not medical, or do not fit the description of a medical experiment as defined below, the consent form or information sheet should include a paragraph giving the same IRB contact information as the Bill of Rights, as follows:

“If you have any questions or comments about participating in this study, you should first talk with the investigator. If for some reason, you do not wish to do this, you may contact the Institutional Review Board, which is concerned with protection of volunteers in research projects. You may reach the IRB office between 9:00 am - 4:00 p.m. Monday to Friday, by calling (415) 600-3688 or by writing: CPMC Research Institute, IRB Office, P.O. Box 7999, SF CA 94120.”

California Assembly Bill 1752: Human Experimentation, which became effective January 1, 1979, provides that all investigators doing a "medical experiment" must offer their subjects a copy of the "Experimental Subject's Bill of Rights". Failure to do so may result in civil or criminal penalties.

A "medical experiment" is defined in the bill as: "The severance or penetration or damaging of tissues of a human subject, or the use of a drug or device as defined in section 26009 of 26010 (of the Health and Safety Code), electromagnetic radiation, heat or cold, or a biological substance or organism, in or upon a human subject in the practice or research of medicine in a manner not reasonably related to maintaining or improving the health of such subject or otherwise directly benefiting such subject..."

The CPMC IRB has interpreted this bill to include almost all studies involving biomedical procedures, placebo control, innovative therapy, and/or normal volunteer subjects. Thus, for these types of studies, the Experimental Subject's Bill of Rights must be given to subjects *along with a copy of the consent form or information sheet for the study*. There should be a reference at the end of the consent form indicating that the subject has received or will receive the Experimental Subject's Bill of Rights.

#### **16. Legally Authorized Representative**

On January 1, 2003 a new California law went into effect which broadened the categories of persons who may act as surrogates to consent for participation in medical research when the subject lacks the capacity to consent. The following is a summary of this new law, which became Health and Safety Code section 24178.

##### Applicability

Before a surrogate can be asked to provide consent, it must be determined that the subject lacks the capacity to consent on his or her own behalf and does not express dissent or resistance to participation in the research. Therefore, prior to relying on a surrogate, the patient's capacity to consent must be assessed and a determination that the patient lacks the capacity to consent must be documented.

The broadened categories of surrogates provided for in the new law apply only where the research relates "to the cognitive impairment, lack of capacity, or serious or life threatening diseases and conditions of the research participant." In situations where the research does not relate to a disease or condition that would qualify above, only a court appointed conservator, guardian or person named pursuant to the Health Care Decisions law can act as a surrogate.

This law **does not apply** to patients who are on an involuntary hold. It **does not apply** to patients admitted to a mental health hospital, either voluntarily, or by a conservator. Note, however, that mental health patients with the capacity to provide informed consent to research may do so.

## **Who Can Provide Surrogate Consent?**

### **Non-Emergency Room Environment**

In a “non-emergency room environment” the surrogate must have reasonable knowledge of the subject. The surrogate may be any of the persons **in the following order of priority**:

1. agent pursuant to an advance health care directive
2. conservator or guardian with authority to make health care decisions
3. spouse
4. registered domestic partners [refer to State of CA Family Code 297]
5. adult children
6. custodial parent
7. adult sibling
8. adult grandchild
9. available adult relative with the closest degree of kinship

The consent of a person with a lower priority cannot supercede the refusal to consent by a person of a higher priority. If there is more than one person in the same order of priority available to give consent and one of them expresses dissent as to participation in the research, consent is deemed not to have been given.

### **Emergency Room Environment**

In an emergency room environment, there is *no* requirement that the decision-maker have a reasonable knowledge of the patient. **The surrogate decision -maker may be any person who falls into categories 1 through 7 above, with no requirement to obtain consent based on priority.**

## **17. Legal Minors**

Special considerations apply when minors (those under 18 years of age) are involved as subjects in research. Children under the age of 7 years would usually not be able to actively participate in the consent process; children between 7 and 12 may be able to participate depending on the complexity of the study procedures and the subject's level of comprehension; and adolescents between 12 and 18 years of age would usually be able to fully participate in the consent process. The consents should be written as "You/your child" and simplified for ease in understanding by minors. Signature lines for both the minor and parent and/or guardian should be included (if applicable).

Specific regulations are set forth by DHHS for obtaining *permission* by parents and guardians, and, except under certain circumstances, *assent* by the children themselves. In general, these conditions provide additional protection for children and, where more than minimal risk is involved, the risk is justified by the anticipated benefit; the relation of the anticipated benefit to risk is at least as favorable to the subjects as that presented by available alternate approaches.

## SECTION 5

### EMERGENCY USE OF AN INVESTIGATIONAL DRUG OR DEVICE

The purpose of these guidelines is to encourage proper use of investigational drugs or devices, and to assure that the patient is protected and receives the best of care. Although FDA regulations require that, in general, clinical investigations of test articles must be reviewed and approved by the IRB before they are conducted, the regulations provide for an exception to this rule in the case of an emergency use of a test article. *For any given institution, this type of exception can be made for emergency use of an investigational drug or device on a **one-time, one-patient basis only**.*

The term "compassionate use" has been used in the past to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or DHHS regulations; its plausible application to various access mechanisms causes more confusion than it does assistance. It is preferable, instead, to use the names of the specific access programs when discussing the use of investigational articles outside of formal clinical trials.

First, the FDA human subjects regulations allow for a test article to be used in emergency situations without prior IRB approval provided that the emergency use is reported to the IRB within five working days; subsequent use of the test article must be reviewed by the IRB (21 CFR 56.104).

*An emergency is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(b)).*

Any such emergency use of a test article is subject to the following conditions, specified in the *Code of Federal Regulations*, Title 21: Food and Drugs:

1. Section 56.102.d. defines "emergency use" as "the use of a test article on a human subject [1] in a life-threatening situation [2] in which no standard acceptable treatment is available, and [3] in which there is not sufficient time to obtain IRB approval."
2. Section 56.104.c. allows for the emergency use of a test article "provided that such emergency use is reported to the IRB within 5 working days. *Any subsequent use of the test article at the institution is subject to IRB review.*"
3. Section 50.23 requires the obtaining of informed consent before the use of the test article unless "both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing" that four conditions have been met:
  - a. The subject is confronted by a life-threatening situation necessitating the use of the test article.
  - b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent.
  - c. Time is not sufficient to obtain informed consent from the subject's legal representative.
  - d. There is no available method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

4. Section 99 states that even for the emergency use of an investigational drug, an Investigational New Drug (IND) exemption is still necessary. In addition, the FDA requires notification for the emergency use of an unapproved Investigational Device.

DHHS regulations require that research involving human participants receive full IRB review and approval, except where expedited review is specifically permitted, prior to initiation of the research (45 CFR 46.103(B)). Physicians do, however, retain the authority to provide emergency medical care to their patients (CFR 46.111(f)). On May 15, 1991, OHRP issued the following statement clarifying emergency treatment of a patient by a physician when that patient is also a research subject:

- a. Whenever emergency care is initiated without prior IRB review and approval, the patient may not be considered to be a research subject. Such emergency care may not be claimed as research, nor may the outcome of such care be included in any report of a research activity. Simply stated: DHHS regulations for the protection of human subjects do not permit research activities to be started, even in an emergency, without prior IRB review and approval.
- b. If the emergency care involves drugs, devices, or biologics that are considered to be investigational by the Food and Drug Administration (FDA), then it may be necessary to meet FDA requirements to use the investigational article for emergency purposes.
- c. Thus, the distinction for DHHS-supported or conducted research is that while the physician may, without prior IRB approval, treat the patient/subject using a test article (if the situation meets the FDA requirements), the subject may not be considered a research subject; data derived from use of the test article may not be used in the study.

- **Procedures for Use**

In order to approve the emergency use of a drug or device as expeditiously as possible, while maintaining compliance with federal regulations, the CPMC Institutional Review Board (IRB) asks that the following procedures be followed:

**Prior to Emergency Use:**

1. The investigator contacts the manufacturer or FDA to determine if the drug/device can be made available for the emergency use under the company's IND/IDE. The investigator arranges for shipment of the drug or device and obtains the IND/IDE number.

**Note:** Some manufacturers will agree to allow the use of the test article, but may require an IRB approval letter before the test article will be shipped. If there is insufficient time for this, the investigator contacts the IRB Chair, who will then prepare a written statement to indicate that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104 (c). An acknowledgment letter has been acceptable to manufacturers who have allowed shipments to proceed under these circumstances.

2. The investigator contacts the IRB Chair to notify of the prospective emergency use of the test article. This is intended for purposes of discussing the circumstances for the use, to determine if use should proceed prior to IRB review, to initiate tracking and to ensure that the investigator files a report within the five day time-frame required by the FDA regulations. If conditions for emergency use are met and it is not possible to convene a quorum within the time available, the use may proceed without IRB approval. **Emergency authorization is for one time, one subject only.**
3. The investigator completes and submits **within five (5) working days** this form following emergency use of the test article.
4. The investigator obtains any approvals or notifications required by his/her department or facility.
5. For drugs administered at this facility, the research pharmacist is notified by the investigator after obtaining IRB approval.
6. Having completed steps 1 through 5, the drug or device may be used on an emergency basis for one subject only.

#### **Following Emergency Use:**

1. Within five (5) working days after the emergency use of the drug/device, the investigator completes the IRB form, and submits it to the IRB, along with the signed consent form. **This is a requirement of the FDA.**
2. The Form and consent form are reviewed at the next convened meeting of the IRB.
3. The emergency use is noted in the minutes of the meeting of the IRB.

- **Considerations for Future Requests**

Because the FDA expects physicians "to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements...far enough in advance," the IRB recommends that once a drug or device has been used on an emergency basis, a protocol should be developed for future use. The IRB will help physicians handle emergency situations as quickly as possible; however, the Committee is restricted by the federal regulation that allows approval for emergency use of a test article for *one patient, one time only, per institution*.

## ADDITIONAL GUIDANCE FROM FDA

### Emergency Use of an Investigational Drug or Device

#### **1. Obtaining an Emergency IND**

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means.

#### **2. Exemption from Prospective IRB Approval**

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless the subject is in a life threatening or severely debilitating situation in which no standard acceptable treatment is available, allows for one emergency use of a test article without prospective IRB review. Life threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life threatening do not require the condition to be immediately life threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Not all emergency use requires an exemption from prospective IRB review. When there is time for prospective IRB approval, the IRB expects the investigator to complete a New Project application describing the emergency use. The application will be scheduled for review at the next IRB meeting (IRB-01 meets every week). The FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. Therefore, if the first use does not have prospective review, the IRB notifies the investigator that if it is possible subsequent use of the agent will occur; a New Project application should be submitted for IRB review immediately following the first emergency use. The FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

The investigator should notify the IRB chair prior to the emergency use; however, this notification should not be construed as IRB approval. The investigator is required to file a written report within five working days, and notifying the chair is used to initiate tracking to ensure that the investigator files this report as required by 21 CFR 56.104(c).

The FDA regulations do not provide for expedited IRB approval in emergency situations. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, the IRB-01 chair will send the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although this is not an "IRB approval," the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

### **3. Exception from Informed Consent Requirement**

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained 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.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article.

## SECTION 6

### MEDICAL DEVICES SIGNIFICANT AND NON-SIGNIFICANT RISK DEVICE STUDIES (Per 21 CFR Parts 812, 813 and Parts 50, 56)

FDA's Investigational Device Exemption (IDE) regulation recognizes two types of investigations based on risk-significant and nonsignificant. Significant risk device investigations are subject to all the requirements of the IDE regulation while nonsignificant risk device investigations are subject to the abbreviated requirements. Generally, this difference involves the approval process and the responsibility of the participants for making reports and keeping records; all other requirements are the same.

- **Determination of Significant or Nonsignificant Risk**

The sponsor makes the initial determination of whether or not the proposed device investigation presents a significant risk to the health, safety, or welfare of the subject. The IDE regulation defines a significant risk device as an investigational device that presents a potential for serious risk to the health, safety, or welfare of a subject and that is:

1. an implant;
2. for use in supporting or sustaining human life; or
3. substantially important in diagnosing, curing, mitigating or treating disease, or in preventing impairment of human health.

- **Approval Process**

In accordance with the CPMC Sutter/CHS Policy Guidelines on accuracy in billing government programs and third party payers, it is mandatory that investigators notify CPMC's Research Institute when an investigational device is planned for use prior to submitting the study to the IRB. The 'Request for Investigational Device Use in a Patient Setting' form is to be completed and three (3) copies given to the IRB with the protocol submission. Provided with the forms are instructions for completion; contact the Director of Clinical Research (415-600-3014) for further information.

**Significant risk device investigations** are subject to the full requirements of the IDE regulation, while the abbreviated requirements apply to nonsignificant risk device investigations. The major differences between the full and abbreviated requirements of the IDE regulation are the procedure to obtain approval and the recordkeeping and reporting requirements.

Investigation can begin after the sponsor obtains both FDA and IRB approval for a significant risk investigation.

**For a nonsignificant risk device investigation**, the investigator (and sponsor) presents the proposed study to the Institutional Review Board (IRB) along with a report of prior investigations and the investigational plan. The investigational plan will include such information as the purpose of the study, a written protocol, a risk analysis and description of patient selection, a description of the device, monitoring procedures, labeling, and consent materials. In addition, the sponsor must present to the IRB a statement of why the investigation does not pose a significant risk.

If the IRB approves the investigation as nonsignificant risk at its institution, the investigation is considered to have an approved IDE under the abbreviated requirements of the IDE regulation and can begin immediately. FDA is not involved in the approval process and is normally not aware of the study. If the IRB determines, however, that the proposed investigation is a significant risk device investigation, a different approval process is required. In this case, the sponsor must submit an IDE application to the FDA and the proposed investigation may be subject to the full requirements of the IDE regulation.

#### **When can an investigation begin?**

- for a significant risk device (SR) - after FDA-IDE and IRB approval
- for a nonsignificant risk device (NSR) - after IRB approval;

- **The IRB Decision Making Process**

An IRB must make two separate decisions.

**First**, is the device designated as SR or NSR?

**Second**, is the investigation approvable or not? The criteria for the two decisions are different.

- **NSR/SR Decision**

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor believes that a study is NSR, the sponsor should provide an IRB with the study proposal, an explanation of why the study is NSR, and other supporting information, e.g., any reports of prior investigations. The sponsor should also tell the IRB if the FDA or any other IRB has determined that the study will be SR or NSR, and provide any other information requested by the IRB. The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees, the investigation may begin without submission of an IDE application to FDA. If the IRB disagrees, the study can only be conducted at that IRB's institution as a SR investigation and the sponsor must notify FDA that a SR determination has been made (whether or not the sponsor ultimately conducts the study at that institution).

The sponsor and the IRB should understand that a study with "a potential for serious risk" is one that presents a potential for serious harm. Thus, to determine if a study is a SR, an IRB must consider the nature of the harm that may result from use of the device. If the device being investigated might cause significant harm to any of the subjects, the study should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB should consider the potential harm that could be caused by the procedure as well as the potential harm caused by the device. Those investigations where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure are included among those studies that are SR.

While the IRB normally serves as the FDA's surrogate with respect to the review and approval of NSR studies, the ultimate decision in determining if a device study is SR or NSR is the FDA's. On some occasions, the FDA may overrule an IRB's decision that a device study presents NSR or SR. When the FDA overrules an IRB's NSR determination, an IDE application must be submitted to the FDA. On the other hand, when the FDA considers the device study to be NSR, the FDA may return an IDE application to the sponsor, and the IRB must then determine if it wants the study to take place in its institution as a NSR investigation.

- **The Decision to Approve or Disapprove**

Once a decision on the degree of risk has been reached, the IRB should consider whether the study should be approved or not. Generally, full IRB review is required when reviewing both SR and NSR studies. Some NSR studies, however, may also be considered minimal risk, i.e., the risk is no greater than that encountered in daily activities, and the IRB may choose to review those under its expedited review procedures.

Minor changes in already approved studies may also be reviewed through the expedited review procedure.

The criteria for deciding if either a SR or NSR study should be approved are the same as those used to evaluate research involving any FDA regulated product. The IRB should determine that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of patients are acceptable. To determine that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses SR or NSR. That decision is based upon the seriousness of the harm that may result for the use of the device.

## SECTION 7

### VULNERABLE POPULATIONS

There are a number of research populations described in the federal regulations as "vulnerable" or that requires additional safeguards or protection. "Vulnerable" or special classes of subjects include children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons [45 CFR 46.111]. In addition, the regulations outline specific provisions for research involving fetuses, pregnant women, and human in vitro fertilization [45 CFR 46 Subpart B]; prisoners [45 CFR 46 Subpart C]; and children [45 CFR 46 Subpart D].

**Exemption from Committee review does not apply to research involving vulnerable populations or special classes of subjects.**

- **Children or Minors**

Federal regulations permit IRBs to approve a research project involving minors ((in California, those under the age of 18 years old) after determining which of the following categories applies, and only if the project satisfies all of the conditions in the applicable category (45 CFR 46, Subpart D) :

1. Research that does not involve greater than minimal risk may be approved if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians. The IRB generally finds that permission of one parent or guardian is sufficient.
2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject, or a monitoring procedure that is likely to contribute to the subject's well-being, may be approved if the IRB finds that:
  - the risk is justified by the anticipated benefit to the subject;
  - the relationship of anticipated benefit to risk is at least as favorable as that presented by available alternative approaches; and
  - adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. The IRB generally finds that permission of one parent or guardian is sufficient.
3. Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, may be approved if the IRB finds that:
  - the risk represents a minor increase over minimal risk;
  - the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
  - the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition; and
  - adequate provisions are made for soliciting assent of the children and permission of their parents or guardians. The IRB generally finds that permission of both parents is required, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.
4. Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved if the IRB and the Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, find that:

- the research in fact satisfies one of the above three conditions; or
- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles; and
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

## **Definitions**

**Assent:** A child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent (45 CFR 46.402(b)).

**Benefit:** A valued or desired outcome; an advantage.

**Children:** Persons who have not attained the legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted (45 CFR 46.402(a)).

**Emancipated Minor:** A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation. (See also: *Mature Minor*.)

**Guardian:** An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care (45 CFR 46.402(3)).

**Mature Minor:** Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor. (See also: *Emancipated Minor*.)

**Minimal Risk:** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (Federal Policy 46.102(i)). For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

**Permission:** The agreement of parent(s) or guardian to the participation of their child or ward in research (45 CFR 46.402(c)).

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

**Phase 1 Trials.** The issue of Phase 1 drug studies deserves special consideration. The usual approach to designing drug studies involving children as subjects is for appropriate studies to be conducted first in animals, adults, and older children before young children are involved as research subjects. There are some studies, however, in which data may not be entirely generalizable from older populations, and in which the existence of life-threatening conditions for children are important considerations in the IRB's risk/benefit analysis. The requirement for previous testing in adults or older children may thus not be appropriate.

Furthermore, some diseases specific to children may require that children be involved without data from older groups (e.g., there is no adult model that mimics the state of HIV-infected newborns; Wilms' tumor and various cancers such as neuroblastoma affect infants who do not survive into older childhood.) In some cases "tandem" studies in older populations and children may be justifiable. For example, some Phase 1 studies in children might be based on only pharmacological safety and toxicity data (completed Phase 1 and ongoing Phase 2) but without complete effectiveness data from trials in adults and older children. If the IRB approves a Phase 1 drug trial, the consent document must specify what is known about the probability that, and the degree to which, an intervention will be of possible benefit based on all of these data.

### **Consent Procedures**

When children or minors are involved in research, the regulations require the assent of the child or minor and the permission of the parent(s), in place of the consent of the subjects.

When children are involved in research, the regulations require the *assent* (knowledgeable agreement) of the child, in addition to the permission of the parent(s). Children should be asked whether or not they wish to participate in the research. The IRB determines whether all or some of the children are capable of assenting. It may often be difficult to assess the capacity of children for actively participating in the consent process. However, the IRB uses the general guideline that children under the age of 7 years would usually not be able to do so; children between the age of 7 and 12 years old may be able to do so, depending on the complexity of the study procedures and the individual subject's level of comprehension; and adolescents between 12 and 18 years of age would usually be able to fully participate in the consent process. The IRB generally finds that permission of both parents is required, unless one parent is deceased, unknown, incompetent, or not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

### **Exemption from Review**

The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children covered by Subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed. The remaining exemptions in 45 CFR 46.101 (b) (2) apply to research involving children.

- **Wards of the State**

The special protections for children set forth in Subpart D include additional limitations on some research involving children who are wards of the state or any other agency, institution, or entity. Where the research involves greater than minimal risk to the subjects with no prospect of direct benefit to individual subjects (45 CFR 46.406), or requires HHS Secretarial approval (45 CFR 46.407), the research must either be related to their status as wards, or else be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards (45 CFR 46.409). The IRB must require, for each child who is a ward, appointment of an advocate in addition to any other individual acting on behalf of the child as a guardian or *in loco parentis*.

IRBs should be particularly concerned with the involvement of HIV-infected children who are in foster care, but who are also not wards. Many of these children are from racial or ethnic minorities. IRBs need to give special attention to groups of children such as these who, while they need special protections, should not be denied the opportunity to participate in research that may potentially be of benefit to them.

Finally, whenever institutionalized children might be involved in research, care should be taken to ensure that they are not included as participants simply because of their availability to the investigator.

### CA Penal Code sections 11160-11163.5.

The following guidelines have been incorporated in the informed consent templates in order to comply with CA Penal Code sections 11160-11163.5. The State of California mandates that investigators and their staff report a reasonable suspicion or known abuse or neglect of a child (CA Penal Code Section 11160-11163.5). When research is likely to reveal possible child abuse, such as interviews about personal behavior, practices, discipline, relationships, etc. **or when research is conducted in the subject's home, medical facility, or a doctor's office,** the consent should clearly indicate that the investigator is required to report a reasonable suspicion or known abuse or neglect of a child. The following sample is meant to guide the investigator:

“Under California law, the privilege of confidentiality does not include information about sexual or physical abuse of a child. If any member of the research team has or is given such information, she or he is required to report it to the authorities. The obligation to report includes alleged or probable abuse as well as known abuse.”

CPMC IRB acknowledges the sensitivity of the wording and will consider alternative wording suggested by the investigator as long as the limits on maintaining the child's confidentiality are made clear.

- **Pregnant Women, Human Fetuses and Neonates**

Federal regulations require that IRBs require additional safeguards before approving research involving fetuses, pregnant women, or in vitro fertilization (45 CFR 46, Subpart B).

An IRB may approve research directed involving pregnant women or fetuses if the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means. If the research holds out the prospect of direct benefit solely to the fetus, then both the pregnant woman and the father must give informed consent unless he is unavailable, incompetent, temporarily incapacitated, or the pregnancy resulted from rape or incest.

In general, neonates of uncertain viability may be involved in research if the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or if the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research. In either case, the consent of either parent is required.

In general, nonviable neonates may be involved in research if the vital functions of the neonate will not be artificially maintained, the research will not terminate the heartbeat or respiration of the neonate, there is no added risk to the neonate from the research, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means. Consent of both parents is generally required.

Research involving human fetal tissue (placenta, or tissue from a spontaneous or induced abortion or from a still birth) is evaluated as tissue specimen research, using the guidelines for research involving specimens.

Studies using human fetal tissue for transplantation research and studies of human embryos involve very explicit regulations concerning consent and study procedures. Investigators wishing to conduct transplantation research with human fetal tissue should contact the IRB Office well in advance of IRB application submission to discuss applicable regulations.

## Definitions

**Dead Fetus:** An expelled or delivered fetus that exhibits no heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached) (45 CFR 46.203(f)). Generally, some organs, tissues, and cells, (referred to collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

**Fetal Material:** The placenta, amniotic fluid, fetal membranes, and the umbilical cord.

**Fetus:** The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant (45 CFR 46.203(c)). (Hereafter, the term "fetus" will refer to a living fetus unless otherwise specified). The term "fetus" generally refers to later phases of development; the term "embryo" is usually used for earlier phases of development.

**Human In Vitro Fertilization:** Any fertilization involving human sperm and ova that occur outside the human body.

**Minimal Risk:** A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (Federal Policy 46.102(i)). For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

**Nonviable Fetus:** An expelled or delivered fetus which, although it is living, cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age less than 20 weeks and weight less than 500 grams (Federal Register 40 (August 8, 1975): 33552), a specific determination as to viability must be made by a physician in each instance.

**Pregnancy:** The period from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (i.e., has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test (45 CFR 46.203(b)). This "conformation" may be in error, but, for research purposes, investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

**Viable Infant:** When referring to a delivered or expelled fetus, the term "viable infant" means likely to survive to the point of sustaining life independently, given the benefit of available medical therapy. This judgment is made by a physician. In accordance with DHHS regulations, the Secretary, HHS, may publish guidelines to assist in the determination of viability. Such guidelines were published in 1975, and specify an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more as indices of fetal viability (Federal Register 40 (August 8, 1975): 33552). These indices depend on the state of present technology and may be revised periodically.

## **General Limitations [46-206]**

1. No activity to which this subpart is applicable may be undertaken unless:
  - Appropriate studies on animals and non-pregnant individuals have been completed.
  - Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.
  - Individuals engaged in the activity will have no part in 1) any decisions as to the timing, method, and procedures used to terminate the pregnancy, and 2) determining the viability of the fetus at the termination of the pregnancy.
  - No procedural changes which may cause greater than minimal risk to the fetus or the pregnant women will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.
2. No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

### **• Fetuses *In Utero* as Subjects [46-208]**

1. No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless:
  - the purpose of the activity is to *meet the health needs of the particular fetus* and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or
  - the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.
2. The research activity may be conducted only if the mother and father are legally competent and have given their informed consent (See full regulations for exceptions regarding the father's informed consent)

### **• Fetuses *Ex Utero*, Including Nonviable Fetuses, as Subjects [46-210]**

1. Until it has been ascertained whether or not a fetus *ex utero* is viable, a fetus *ex utero* may not be involved as a subject in an activity covered by this subpart unless:
  - There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means;
  - The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.
2. No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:
  - Vital functions of the fetus will not be artificially maintained,
  - Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and
  - The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.
3. In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.
4. An activity permitted under paragraph 1 or 2 of this section may be conducted only if the mother and father are legally competent and have given their full informed consent.

- **The Dead Fetus, Fetal Material, or the Placenta [46.210]**

Activities involving the dead fetus, mascerated fetal material, or cells, tissues, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

- **In-Vitro Fertilization [46.204(d)]**

One issue of importance to IRBs is "the problem of spare embryos". IRBs need to assure that investigators have clearly addressed what will happen to embryos that are not used in the particular, embryo transfer procedure for which they were created (e.g., if they (will) be used for research purposes, they (will) be implanted in the uterus of another woman, or they (will) be destroyed); investigators should ensure that participants are informed of and consent, in writing, to the resolution of this question. Investigators should also clarify to participants the ownership of the embryos that are not used in the procedure (e.g., that they "belong" to the laboratory and may not be removed by the parents, or that they "belong" to the biological mother).

- **Fetal Tissue Transplantation [FR 58 8/30/93]**

On January 22, 1993, President Clinton issued a directive to the Secretary of Health and Human Services ending a five-year moratorium on Federal funding of therapeutic transplantation research that uses human fetal tissue derived from induced abortions. Section 498 A of the Public Health Service Act (42 U.S.C. 289g-1) added by Public Law 103-43, the NIH Revitalization Act of 1993 provisions pertinent to research on transplantation of fetal tissue are summarized as follows:

- Human fetal tissue means tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth.
- Human fetal tissue may be used regardless of whether the tissue is obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth.
- The Secretary of Health and Human Services may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes.
- The woman donating the human fetal tissue must sign a statement declaring that the tissue is being donated for therapeutic transplantation research, the donation is being made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue, and the donation is being made without her (the donor) having been informed of the identity of those individuals who may be the recipients.
- The attending physician must sign a statement declaring that the tissue has been obtained in accord with the donor's signed statement and that full disclosure has been made to the donating women of: 1) The attending physician's interest, if any, in the research to be conducted with the tissue, and 2) any known medical risks to the donor or risks to her privacy that might be associated with the donation of the tissue and are in addition to the risks associated with the woman's medical care.

- The individual with the principal responsibility for conducting the research must sign a statement declaring that the individual is aware that the tissue is human fetal tissue donated for research purposes and may have been obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth; that the principally responsible researcher will require, prior to obtaining the consent of a person to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of the foregoing information by such recipient; and that the principally responsible researcher has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purposes of the research.

- **Prisoners**

Because incarceration could affect a person's ability to make a truly voluntary and uncoerced decision whether or not to participate in a research project, the federal regulations provide additional safeguards for the protection of prisoners (45 CFR 46, Subpart C). A prisoner is defined as any individual involuntarily confined or detained in a penal institution. This definition includes individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Any project that recruits prisoners must be reviewed at a full IRB meeting with a prisoner advocate present. If the project was not initially approved to recruit prisoners, then the investigator may not enroll a prisoner (e.g., a prisoner who is brought to CPMC for treatment who happens to be eligible for a research study may not be enrolled unless the project was reviewed at a full board meeting with a prisoner advocate present.)

The prisoner rules also apply for a subject who at a later date becomes a prisoner, because it is unlikely that the IRB review of the research project contemplated the constraints imposed by incarceration. Therefore, if an investigator determines that a subject has become a prisoner at some later date after enrollment, and the study involves additional research interventions or interactions with that subject, the subject must either be dropped from follow-up, or a protocol modification request must be submitted requesting review for inclusion of prisoners as subjects.

When a prisoner is a subject, in addition to the usual criteria for approval, the IRB must find that:

1. the research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);
2. any possible advantages accruing to the prisoner through his or her participation in the research, when compared to 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;
3. the risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
4. procedures for the selection of 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;

5. the information is presented in language which is understandable to the subject population;
6. 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
7. where the IRB 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 prisoners' sentences, and for informing participants of this fact.

Four categories of research involving prisoners are permitted under the federal regulations. They are:

1. studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
2. studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
3. research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere); and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults; or
4. research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject.

The informed consent document must include additional information for potential subjects regarding the fact that participation or non-participation will have no effect on the duration of incarceration or terms of parole.

### **Definitions**

**Minimal Risk:** Risk of physical or psychological harm that is no greater in probability and severity than that ordinarily encountered in the daily lives, or in the routine medical, dental or psychological examinations of healthy persons (45 CFR 303 (d)). IRBs should note that this definition differs somewhat from that given for noninstitutionalized, competent adults (Federal Policy 45 CFR 46.102(i))

**Prisoner:** An individual involuntarily confined in a penal institution, including persons: 1) sentenced under a criminal or civil statute; 2) detained pending arraignment, trial, or sentencing; and 3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration a penal institution (45 CFR 46.303(c)).

## **Cognitively Impaired Persons**

Individuals in a wide variety of situations may have impaired decision-making capacity. For example, impairment may occur at times of great stress. Impaired capacity is not limited to individuals with neurologic, psychiatric, or substance abuse problems; conversely, individuals with neurologic, psychiatric, or substance abuse problems should not be presumed to be decisionally impaired. Some research questions may be answered only by research that involves persons with impaired decision making capacity; precluding this research would contribute to needless suffering. The most severely impaired individuals have the greatest need for the benefits of research on etiology and treatment. While this area is controversial, limiting research to the least impaired individuals would hamper research on the underlying causes and potential therapies of many disorders. Not all research will directly benefit the individual participant but may offer future benefits to others who have or will develop the condition or disorder. For example, genetic studies, biochemical measures, or other non-therapeutic approaches may benefit subsequent generations.

Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired. While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population.

The NIH offers the following points to consider to assist IRBs and clinical investigators in their effort to protect participants in research who are, or may be, or may become decisionally impaired:

### **Conflicting Roles and Potential Conflicts of Interest**

Potential and actual research subjects, especially those with permanent or transient cognitive impairments, may find it difficult to understand the difference between research and treatment, and to understand researchers' multiple roles, making "therapeutic misconceptions" particularly problematic and possibly creating confusion among participants and their families.

It is essential that the consent process (including consent documents) clearly indicate differences both between individualized treatment and research and between clinician and clinical investigator.

### **Assessing Capacity to Consent**

Individual's capacities, impairments, and needs must be taken into account in order to develop practical and ethical approaches to enable them to participate in research. A clear understanding of the implications of various cognitive impairments, along with a careful consideration of proposed clinical research methodology, is required. Assessment is complex; simply answering a certain number of factual questions about a protocol may not be an adequate assessment. A key factor in subject's decision making is their appreciation of how the risks, benefits, and alternatives to participation in the study apply to them personally.

Limited decision-making capacity covers a broad spectrum. A healthy person in shock may be temporarily decisionally impaired. Another may have been severely mentally retarded since birth, while yet a third who has schizophrenia may have fluctuating capacity. Researchers should be sensitive to the differing levels of capacity and use assessment methods tailored to the specific situation. Further, researchers should carefully consider the timing of assessment to avoid periods of heightened vulnerability when individuals may not be able to provide valid informed consent.

Both IRBs and clinical investigators must keep in mind that decision-making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing. The IRB, at its discretion, may require an outside witness to observe the consent process.

Because no generally accepted criteria for determining competence to consent to research exists for persons whose mental status is uncertain or fluctuating, the role of the IRB in assessing the criteria proposed by the investigator is of major importance. The selection of an appropriate representative to consent on behalf of those unable to consent for themselves must be accomplished without clear guidance from statutes, case law, or regulations.

### **Comprehension**

The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the clinician/investigator. In most cases, it will be the clinician/investigator who is in the ideal position to evaluate the subject's ability to understand the implications of the research and whether the subject is making a rational decision to participate. Likewise, in most studies it is the clinician/investigator who can best make a judgment of the subject's ability to understand and follow the protocol.

In developing the consenting process, the investigator is obligated to incorporate any special accommodations necessary to assure that the subject population or their surrogates comprehend the nature and purpose of the study. Useful techniques may include simplified consent documents, supplemental summary sheets, formal Q&A sessions for the subject and family or friends, and waiting periods after the initial discussion before the prospective subject actually enrolls.

### **Voluntary Agreement**

Closely related to the determination of the ability to comprehend the nature of the study is the importance of ensuring that subjects' participation is completely voluntary. Some knowledge and assessment of the subject's competence is relevant to a determination of whether voluntary participation is evidenced by a written consent, or in the case of persons lacking legal capacity to consent, their assent. Research should not be conducted against the wishes of the subject, and making certain that the written documents are indeed a reflection of reality is the function of the individual researcher and the IRB.

## Second Signature on the Consent Document

There are many situations in which a subject should be encouraged to authorize the involvement of family members. However, the consent of another party will be required only when the patient is determined to lack the legal ability to provide an informed consent. This would include minors (persons under the age of 18) and persons adjudicated incompetent. This also includes persons who are not capable of understanding the nature of their illness or the risks, benefits, and natural consequences of participation. Investigators are reminded to check with the IRB regarding California State laws on legally authorized representative requirements.

## Definitions

**Cognitively Impaired:** Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders), an organic impairment (e.g., dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

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

Competence may fluctuate as a function of the natural course of a mental illness, response to treatment, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically. As a designation of legal status, competence or incompetence pertains to adjudication in court proceedings that a person's abilities are so diminished that his or her decisions or actions (e.g., writing a will) should have no legal effect. Such adjudications are often determined by inability to manage business or monetary affairs and do not necessarily reflect a person's ability to function in other situations.

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

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

**Institution:** A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care). Examples include general, mental, or chronic disease hospitals; inpatient community mental health centers; halfway houses and nursing homes; alcohol and drug addiction treatment centers; homes for the aged or dependent, residential schools for the mentally or physically handicapped; and homes for dependent and neglected children.

**Selection of Subjects.** Research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Persons who are institutionalized, particularly if disabled, should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researcher.

**Degree of Risk:** No clear consensus exists on the acceptable degree of risk when mentally compromised persons are involved in the research. One position holds that research that presents more than minimal risk should involve mentally compromised persons only if they will derive a direct and significant benefit from participation. The National Commission recommended that a minor increase over **Minimal risk** may be permitted in research involving those institutionalized as mentally disabled, but only where the research is designed to evaluate an intervention of foreseeable benefit to their care. For research that does not involve beneficial interventions and that presents more than minimal risk, the National Commission recommended that the anticipated knowledge sought should be of vital importance for understanding or eventually alleviating the subject's disorder or condition. Finally, the National Commission recommended that there be additional ethical review at the national level for research projects the IRB believes should be supported because the knowledge to be gained may be of major significance to the prevention, diagnosis, or treatment of mental disorders - but that would not otherwise be approved at the local level. Since the mechanism of a national board is not currently available, the IRB will consider obtaining assistance from expert consultants.

**Limiting Risks.** A description of appropriate psychological or medical screening criteria to prevent or reduce the chances of adverse reactions to the therapeutic and research procedures must be included. The IRB might require that other health care providers be consulted to ensure that proposed research procedures will not be detrimental to ongoing therapeutic regimens. Specific diagnostic, symptomatic, and demographic criteria for subject recruitment should be described in the research proposal

Any plan to hospitalize subjects or extend hospitalization for research purposes should be justified by the investigator. The effects of separation from supportive family or friends, of disruption in schooling or employment, and the question of responsibility for bearing any additional costs should be carefully considered by the IRB. Methods for assuring adequate protections for the **privacy** of the subjects and the **confidentiality** of the information gathered should also be described by the investigator. Individually identifiable information that is "sensitive" should be safeguarded, and requests for the release of such information to others, for research or auditing, should be allowed only when continued confidentiality is guaranteed.

#### **NIH Revitalization Act of 1993- Policy-Effective June 1, 1994**

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

- **Clinical Trials**

Under the statute, when a Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important gender or race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

As such, investigators must consider the following when planning a Phase III clinical trial for NIH support.

1. If the data from prior studies strongly indicate the existence of significant differences of clinical or public health importance in intervention effect among subgroups (gender and/or racial/ethnic subgroups), the primary question(s) to be addressed by the proposed Phase III trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.
2. If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect between subgroups, then gender or race/ethnicity will not be required as subject selection criteria. However, the inclusion of gender or racial/ethnic subgroups is still strongly encouraged.
3. If the data from prior studies neither support strongly nor negate strongly the existence of significant differences of clinical or public health importance in intervention effect between subgroups, then the Phase III trial will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups, so that valid analysis of the intervention effect in subgroups can be performed. However, the trial will not be required to provide high statistical power for each subgroup.

Cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

- **HIV-Infected Individuals [45 CFR 46.116 and 117 and 21 CFR 50.25]**

Individuals who are infected with the Human Immunodeficiency Virus (HIV) are a particularly vulnerable subject group. The fact that they suffer or may eventually suffer from a fatal disease with no currently known cure may compromise their ability to freely give or refuse consent to participate in research projects. The IRB will therefore give special attention to certain issues for these individuals, such as assessing the potential risk/benefit balance of the study and assuring that the consent process clearly distinguishes experimental procedures from clinical care.

Testing for HIV-antibody, which establishes that an individual has been exposed to the HIV virus, involves unique concerns when it is done for research purposes. The primary concerns for the IRB revolve around two sets of issues. One is the complex set of risks associated with a subject learning that he or she is HIV positive, particularly if the results are unexpected. The other issue is the risk of loss of confidentiality of the research record which is created when such testing is done as part of a study. Thus, if HIV-antibody testing is to be performed for research purposes, the following should also occur:

1. The appropriate box must be checked on the IRB Cover Page.
2. Both the protocol and consent form must state that the HIV testing is being performed for purposes of the study.
3. The protocol must include a justification as to why this testing is being performed.
4. Pre- and post-test counseling of the subjects by qualified personnel must be performed and the subjects must be informed in person of their test results. The subjects should be counseled as to the various risks associated with HIV testing as well as the risks associated with being HIV positive. If the person is HIV positive, the various options available for treatment should be discussed.
5. The details of this counseling (where, when and by whom) should be included in the Procedures section of the consent form.
6. The protocol should discuss how the confidentiality of the HIV-antibody test results will be maintained.

- **California Health and Safety Code Statute**

In 1985, statutory additions were made to the State Health and Safety Code to establish certain requirements regarding mandated blood testing, and *confidentiality* to protect public health. While further revisions of the Code are now under consideration, the current Code contains several points which must be addressed by any investigator doing a research study which includes HIV-antibody testing.

The statute provides for special protection of results of the AIDS antibody test, and prescribes various penalties for the negligent or willful disclosure of identified results unless there is written authorization by the subject to do so. It also specifically forbids HIV-antibody testing without written authorization, and requires the person giving the test to keep the written authorization unless the test is performed at a designated alternate site, on blood or blood products specified by the statute, or on previously stored blood in a blood bank.

Because the statute refers to individually identified test results, it is assumed that none of the protections apply to research records in which no individual is identified.

## SECTION 8

### SPECIAL TOPICS

- **Chart Reviews**

A human subject is defined, in part, as a living individual about whom an investigator conducting research obtains identifiable private information. Therefore, medical or other chart/record review research requires IRB review and approval. The IRB Chair may authorize a waiver of informed consent for chart review research studies if the study is minimal risk, the rights and welfare of the subjects are not adversely affected, the research could not practicably be carried out without the waiver, and, when appropriate, subjects are provided with pertinent information after participation.

Generally, a waiver of consent is granted when all of the chart information that will be used in the research study exists in the medical record prior to the date of the IRB application. If some or all of the chart information that will be used is from hospital visits that occur in the future (e.g., after the date of the IRB application), then consent from some or all subjects may be required. In order to assist the IRB in making the determination for waiver of consent, the investigator should provide the inclusive dates of medical record information that will be used in the study.

In addition to describing the purpose or hypothesis being studied, and the types of analyses that will be done, the investigator should provide the IRB a list of specific variables that will be used from the medical record chart. This could be done in the application itself and by including the data collection sheets that will be used for compiling the chart information.

- **Genetic Research**

DNA projects, by nature of their subject matter, are reviewed for the following information in addition to the standard required review.

Genetic information is uniquely personal information and has the potential to influence employment, insurance, finance, education and possibly self perception. Therefore, genetic information must be carefully maintained in order to protect against stigmatization, discrimination, or significant psychological harm to the subject.

IRB review considers the following issues in both the application and the informed consent document, as applicable:

1. Information that can be obtained from DNA samples in general, and the specific questions to be addressed in this study.
2. The extent of subject and sample confidentiality if the sample and subsequent information will be part of a registry or database.

3. The rights and limitations of subjects to require destruction of their sample and/or associated data at a future date. The rights and limitations of subjects to require that their sample and or associated data be stripped of any identifying information.
4. Identifying information available to other researchers if their sample and/or associated data are part of a registry or database.
5. Mechanisms for maintaining confidentiality in long-term studies, registries, or databases.
6. Potential for commercial profit by the institution, investigator or sponsor from information gathered in this study.
7. The availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on).
8. A clear statement that the sample/data, any cell lines, profits from data etc., are the property of the institution.
9. If genetic information will be disclosed to the subject or another party, the investigator disclosing the information must be named and the specific genetic information being disclosed must be stated.
10. Information disclosed must be in a manner consistent with the recipient's level of knowledge, e.g., information would be phrased differently when disclosed to a layperson versus a physician.
11. Subjects must have the right to decline receiving genetic information.
12. In the absence of a specific authorization to maintain a DNA sample, DNA samples collected and stored or analyzed in connection with a research project shall be destroyed upon completion of the project or withdrawal of the individual from the project. This information must be clearly stated in the informed consent document.

Before involving minors in DNA research, the parent(s) or legal guardian(s) must review and sign the informed consent document. The consent document must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them. Whenever appropriate, the minor's assent should be solicited. Upon reaching the age of majority, if the subject may request his or her information be disclosed that should be included in the consent document. Investigators must follow the appropriate measures with regard to releasing such information (e.g., counseling, etc.).

In some cases it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (paternity or maternity, as could be hidden by adoption or donor fertilization) and other incidental information should not be revealed.

- **Placebo-Controlled Trials**

If an investigator proposes a study in which a placebo is given for any length of time in lieu of an approved FDA indicated drug, the investigator must include risk management procedures in the research plan for the IRB for review. To the extent that the investigator demonstrates that the subject's safety is monitored at all times and provisions are made for immediate rescue if needed, the IRB will consider approval of the study. Once an approval is granted, the investigator is bound to follow the risk management procedures as with any other provision of the approved protocol.

Use of placebos may be appropriate where the investigator demonstrates that:

1. standard therapy is unavailable or is of unproved efficacy, or
2. standard therapy possesses unacceptable side effects, or
3. minimal harm may result from the use of placebo (e.g., ongoing disease has little adverse effect on the patient during the course of the trial and is reversible), or
4. placebo itself may be an effective therapy, or
5. the disease process is characterized by exacerbation and remission.
6. The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:
  - the frequency of monitoring,
  - whether monitoring is in person or by telephone,
  - the criteria for managing a subject in the event of worsening, and
  - how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or withdrawal from the protocol.

The IRB may make its decision based upon the extent to which the above factors are demonstrated and upon a relative weighing of these and other factors. In discussing potential harm from the use of placebos, the investigators must provide a procedure for adequate monitoring of subjects to ensure their safety.

- **Registries**

A research registry is defined as the collection and maintenance of data in which: (1) the individuals in the registry have a common condition, (2) the individuals in the registry may be contacted for future studies, and (3) the names/data of the individuals may be used by investigators other than the original research team. If a registry is being created, the investigator should include the name of the registry, the method of data storage, how subjects are informed of their inclusion in the registry, and how subject identity and information is protected. The informed consent document should inform a potential subject that if s/he decides to participate, his/her name will be stored in a registry and s/he may be contacted in the future by investigators other than the current research team.

Not all compilations of individuals' names and associated data constitute a research registry. A database is not necessarily a registry. The key element in a registry is that names and other identifying information are being stored so that people *other than the original research team* may access the registry information in the future to contact individuals for other studies.

- **Specimens**

Studies involving either existing specimens or prospectively collected specimens require IRB review and approval. Specimen research includes studies of blood samples, other bodily fluids, frozen tissue, or paraffin blocks.

- **Existing Specimens**

Research involving existing specimens (e.g., all specimens are "on the shelf" at the time the application for IRB review is submitted) may be classified as exempt only if there is no link, either in the investigator's records or elsewhere (e.g., pathology department), linking the specimen back to the identity of the subject. Even though it may be difficult or time-consuming to determine the subject's identity, if there is a link, the research cannot be classified as exempt, but may be eligible for a classification of expedited research.

Research involving specimens, all of which have already been obtained at the time of the IRB application, may be eligible for a waiver of consent.

- **Prospectively Collected Specimens**

If the study involves the collection of extra tissue or specimens beyond what is needed for a clinical procedure, IRB review and approval and an informed consent document is required. In such cases, the subject should be informed as to the purpose for obtaining the specimen. If the specimen is going to be retained for future use beyond the purpose of the study for which it was obtained, the subject should be informed regarding who might have future access, for what purposes the specimen might be used, how to request destruction or removal of the specimen from future research use, whether there are plans to compensate the subject should a product be developed.

Specimens (e.g., blood, tissue, and other bodily fluids) collected as part of standard clinical procedures that are unused at the completion of the diagnostic or treatment process and are destined for disposal are often referred to as discarded specimens. The CPMC (hospital) surgical consent form notifies patients that such materials may be discarded or used in research. However, the purpose of the CPMC (hospital) surgical consent form is for a patient to consent to a surgical procedure. It is not intended for or adequate as an informed consent document to participate in research. Therefore, studies involving discarded specimens obtained prospectively may require an informed consent document. As a general rule, if the study requires obtaining other identifiable information about the patient (demographic, diagnostic) for use in the analysis, consent may be required. The IRB Chair may consider waiving informed consent only if the requirements for waiving informed consent are met.

- **Students as Research Subjects**

Consistent with an overall concern that no research subject should be coerced, researchers should take particular precautions to avoid the unintentional or subliminal coercion that may occur when a potential research subject is also a student. For this reason, researchers should avoid using their own students as research subjects. Researchers who wish to use their own students should be able to provide a good scientific reason, rather than convenience, for selecting those students as research subjects. The research project should be relevant to the topic of the class, and participation should be part of the learning experience for the students.

In instances where investigators can provide a good reason for using their own students in their research, the IRB generally requires that someone other than the investigator (or instructor) obtain informed consent and collect the data. When this is not possible, the IRB will consider other methods for obtaining consent and collecting data that would not reveal to the instructor whether or not a student participated in the research project until after final grades have been determined. The students should be informed of what these procedures are in the informed consent document.

- **Surveys, Questionnaires, and Interview Studies**

Not all survey, questionnaire, or interview research is minimal risk. For example, a survey or interview that asks questions about sensitive topics (e.g., childhood abuse, sexual functioning) likely to cause emotional stress or discomfort may require full IRB review.

Some survey research may be classified as exempt from the regulations if the information obtained is recorded in a way that the subject cannot be identified (either directly or through a code numbers or link); in other words, if the research data are anonymous. The term anonymous is sometimes confused with the term confidential. In human subjects research, anonymous means that at no time during the data collection could someone determine who provided the information. If a link existed at any time, even if the link is subsequently destroyed, the IRB cannot consider the information anonymous.

A survey or interview study may also be considered exempt from the regulations even when the data are not anonymous if the information being gathered could not reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.

The most common classification for survey, questionnaire, or interview research is expedited approval. If the study is not anonymous and contains information that, if known, could be damaging as described above, but it does not rise to the level of more than minimal risk, it may be given expedited approval.

For minimal risk mail-out or web-based surveys or questionnaires, it may be appropriate to request that the IRB Chair waive the requirement for the subject's signature on an informed consent document. When the subject's signature requirement is waived, generally the investigator provides all of the required elements of consent in a cover letter, with a statement that returning the survey or questionnaire will be considered voluntary agreement to participate.