Chapter 8
Criteria for IRB Approval of Research

DHHS regulations at 45 CFR 46.111, FDA regulations at 21 CFR 56.111, and the Federal Policy (Common Rule at Section 111) delineate specific criteria for the approval of research. The IRB will determine that all of the following requirements are satisfied before approving proposed research:

A. Risks are minimized through the use of sound research design

B. Risks are reasonable in relation to anticipated benefits

C. The selection of subjects is equitable

D. The informed consent of subjects will be obtained

E. The informed consent of subjects will be documented

F. The research includes adequate provisions for monitoring data to ensure the safety of subjects

G. The research includes adequate provisions to safeguard the confidentiality of data and the privacy of subject

H. The research includes adequate additional protections to safeguard the rights and welfare of subjects who may be vulnerable to coercion or undue influence

I. Risks are Minimized. The IRB must consider the overall level of risk to subjects in evaluating proposed research. In general, the regulations require that the IRB distinguish research that is “greater than minimal risk” from research that is “no greater than minimal risk.” Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent.

Under Federal regulations at 45 CFR 46.102(i), “minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

In order to approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures already being performed on the subjects for diagnostic or treatment purposes.
The IRB is expected to consider the research plan, including the research design and methodology, to determine that there are no flaws that would place subjects at unnecessary risk. When the research design presents unnecessary or unacceptable risks to subjects without commensurate benefits to the subjects or to others, the research cannot ethically proceed and cannot be approved by the IRB.

In order to ascertain whether the research project is adequately designed and thus subjects protected, the IRB reserves the authority to seek opinions from consultants on proposed research and its design. The IRB may determine that proposed research must be re-designed to enhance subject autonomy, maximize benefits, reduce risks, select subjects equitably, minimize undue influence or coercion, or otherwise protect the rights and welfare of human subjects.

The IRB will also consider the qualifications of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges. Overall, the research team must possess the professional and educational qualifications, as well as the resources, to conduct the research project and to protect the rights and welfare of subjects.

II. Psychological and Social Harms. When evaluating research, HSS carefully examines not only the risk of physical harm but also the risk of psychological and social harms.

A. The IRB considers the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.

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

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

In order to mitigate such harms, the IRB reviews proposed research for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in the research.
III. Risks Are Reasonable Relative to Anticipated Benefits. In order to approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects and/or to the importance of the knowledge that may reasonably be expected to result.

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB will consider only those risks that result from the research, and will not consider long range effects (e.g., public policy implications) of applying the knowledge gained in the research.

IV. Selection of Subjects is Equitable. In order to approve research, the IRB must determine that the selection of subjects is equitable. To this end, investigators at HSS, and especially NIH-supported investigators, must provide details of the proposed involvement of humans in research, including the characteristics of the subject population, anticipated numbers, age ranges, and health status. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation.

If ethnic, racial, and gender estimates are not provided as background information for initial review, and enrollment statistics are not provided for continuing review, the investigators must provide a clear rationale for exclusion of this information. For additional information, IRB members and investigators should refer to Section 492B of the Public Health Service Act, and the NIH Guide for Grants and Contracts, Vol. 23, Number 11, March 18, 1994 (see Appendix V).

In making the determination that subject selection is equitable, the IRB will evaluate the purposes of the research and the research setting, and will be especially cognizant of issues involving potentially vulnerable subject populations, which may include children, pregnant women, prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB will carefully examine inclusion-exclusion criteria and recruitment procedures in order to determine that the burdens and benefits of the research are being distributed equitably.

A. Inclusion of Females and Minorities. It is the policy of HSS that females and members of minority groups and their sub-populations should be included in all biomedical and behavioral research projects involving human subjects, unless compelling scientific justification is provided that inclusion is inappropriate with respect to health of the subjects or the purpose of the research.

The IRB will remain mindful of the desirability of including both males and
females as research subjects and will not permit the *arbitrary* exclusion of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

**B. Inclusion of Children.** In June 1996, the American Academy of Pediatrics and the NIH held a joint workshop concerning the participation of children in clinical research. There is valid concern that treatment modalities developed based on research conducted on adults, without adequate data from children, are being used to treat children for many diseases or disorders. Participants in the workshop concluded that there is a sound scientific rationale for including children in research (see Appendix V).

**V. Informed Consent, Parental Permission, and Child Assent Will Be Obtained.** In the order to approved research involving adults as subjects, the IRB must determine that legally effective informed consent will be sought and obtained from each prospective subject or the subject's legally authorized representative (see 45 CFR 46.116 and 21 CFR 50.20), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver or alteration must be consistent with applicable Federal and State laws and regulations.

In order to approve research involving children as subjects, the IRB must determine that the permission of the child’s parent(s) or guardian(s) and the assent of the child will be sought and obtained (or formally waived or altered) in accordance with Subpart D of the HHS and FDA human subject regulations at 45 CFR 46.408 and 21 CFR 50.55, respectively. Any waiver of alteration of these permission or assent requirements must be consistent with applicable Federal and State laws and regulations. Chapter 16 details the requirements for permission and assent relative to the involvement of children in research.

In general,

**A.** The informed consent of an adult subject, the informed consent of a subject’s legally authorized representative, the permission of the parent(s) or guardian(s) of a child-subject or the assent of a child-subject may only be sought under circumstances that minimize the possibility of coercion or undue influence and that provide the parent(s), guardian(s), subject, or legally authorized representative with sufficient opportunity to consider whether or not the subject will participate.

**B.** Information for informed consent, permission, and assent must be presented in language that is understandable to the subject, legally authorized representative, parent(s), or guardian(s).
C. No informed consent, permission, or assent process may include any exculpatory language (i) through which the subject is made to waive, or appear to waive, any of the subject’s legal rights; or (ii) through which the investigator, the sponsor, HSS, or its employees or agents are released from liability for negligence, or appear to be so released.

D. Although it is appropriate for consent, permission or assent documents to state that certain specimens or information may be used for research purposes, using the word “donation” to characterize the future use of specimens or information for research purposes implies abandonment of rights to the “property” donated and will not be approved by the IRB. Whether or not such wording is contained in “the actual informed consent document” is immaterial. All study-related documents must be submitted to the IRB for review. Any separate “donation” agreement for future research use of specimens is regarded to be part of the informed consent documentation and must be in compliance with regulatory requirements.

E. Informed consent, permission, and assent (as applicable) must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.

F. Alternatives to obtaining and documenting informed consent, permission, or assent immediately before the start of the research include obtaining and documenting consent, permission, or assent during a reasonable interval prior to the start of the research that permits the individual sufficient time to make an informed choice about the requested participation. When other alternatives are proposed, the IRB must determine that the alternative is appropriate under Federal and State law and regulation in the jurisdiction in which the subject will be enrolled and participate. These instances will be handled on a case-by-case basis.

VI. Consent Monitoring. In considering the adequacy of informed consent, permission, and assent procedures, the IRB may require special monitoring of the process by an impartial observer (consent monitor) in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

VII. Waiting Periods. In considering the adequacy of informed consent, permission, and assent procedures, the IRB may require that investigators include a “waiting
period” within the process, or employ devices such as audiovisual aids or tests of comprehension.

VIII. Advertisements and Recruitment Incentives. The IRB will review advertisements and recruitment incentives associated with the research that it oversees. Advertisements and incentives are directly related to the informed consent, permission, and assent process and must be consistent with prohibitions on coercion and undue influence.

Any advertisement to recruit subjects should be limited to the information the prospective subjects, legally authorized representatives, parents, or guardians need to determine eligibility and interest. When appropriately worded, the following items may be included:

A. The name and address of the clinical investigator and/or research institution.
B. The condition under study and/or the purpose of the research.
C. In summary form, the criteria that will be used to determine eligibility for the study.
D. A brief list of participation benefits, if any.
E. The time or other commitment required of the subjects.
F. The location of the research and the person or office to contact for further information.

Recruitment procedures must be designed so that informed consent, permission, and assent are given freely and coercion and undue influence are avoided. In order to evaluate this, the IRB must know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

IX. Payments for Research Participation. The IRB will review any proposed payments to research subjects (or their parents, guardians, or legally authorized representatives) associated with the research that it oversees. Payments may not be of such an amount as to result in coercion or undue influence on the decision to participate or continue participation. Payments may not be provided on a schedule that results in coercion or undue influence on the decision to participate or continue participation.

X. Indemnity and Liability Provisions. Subjects in research at HSS may not be asked to waive, or appear to waive, any of their legal rights.

XI. Informed Consent, Permission, and Assent will be Documented. In order to approve research, the IRB must determine that informed consent of adult subjects (or
the subject’s legally authorized representative) and/or the permission of the parent(s) or guardian(s) of child subjects, will be documented in writing, unless documentation can be waived under Federal regulations. Chapter 16 details the requirements for documentation of permission for the involvement of children in research.

The method of documenting the assent of child subjects will be determined by the IRB in accordance with Subpart D of the DHHS and FDA regulations at 45 CFR 46.408 and 21 CFR 50.55, respectively. Chapter 16 details the requirements for documentation of child assent.

A. **Long Form vs Short Form Documentation.** Federal regulations at 45 CFR 46.117 and 21 CFR 50.27 provide two methods for documenting informed consent and/or permission:

(i) Consent or permission may be documented through use of a written document that embodies all of the required elements of informed consent. The document must be signed by the subject (or the subject’s legally authorized representative, parent(s) or guardian(s) in compliance with all regulatory requirements), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated; and

(ii) Consent or permission may also be documented through use of a short form document which states that the elements of informed consent have been presented orally to the subject (or the legally authorized representative, parent(s) or guardian(s) in compliance with all regulatory requirements). When this method is used, (i) there must be a witness to the oral presentation; (ii) the IRB must approve a written summary of what is to be presented orally; (iii) only the short form must be signed by the subject, representative, parent(s), or guardian(s); (iv) the witness must sign both the short form and the summary; (v) the person actually obtaining consent must sign the summary; and (vi) a copy of the summary and the short form will be given to the subject, the representative, the parent(s) or guardian(s).

B. **Illiterate Subjects.** Illiterate persons may have informed consent or permission information read to them and may “make their mark” in a manner consistent with the laws of New York (or other State in which the research is conducted) to document their understanding. In this situation, it is also desirable to obtain the signature of a witness to the process and the signature of the person conducting the consent or permission interview.

C. **Witness Signature.** Where it deems warranted, the IRB may require the signature of a witness who has been present during the entire consent or permission interview and who can attest to the accuracy of the presentation.
and the apparent understanding of the subject, representative, parent(s) or guardian(s), on the informed consent or permission document. Such attestation will be noted in writing on the document. The witness is also present to attest to the validity of the individual’s signature.

D. **Date Stamp Required.** All informed consent and permission documents will have a date stamp indicating the beginning and end of the approval period during which the document may be used to obtain consent or permission. Only the stamped IRB-approved informed consent or permission document can be used for the informed consent or permission process. The investigator is responsible for storing signed informed consent and permission documents for at least three years following the completion of the research.

E. **Copy to Decision-Maker is Required.** Once the informed consent or permission information has been presented, the informed consent or permission document is given to the subject, legally authorized representative, parent(s) or guardian(s) for further review. The individual making the participation decision may take the document home to discuss the matter with family, friends, spouses, or other professionals. When the subject, representative, parent(s) or guardian(s) decide(s) that the subject will enter the study, he/she/they sign(s) and date(s) the informed consent or permission document.

XII. **Safety Monitoring Is Adequate.** In order to approve research, the IRB must determine that, where appropriate, the research plan makes adequate provision for monitoring the data to protect the safety of subjects. For research in which risks are substantial, a detailed description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events.

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) to be established for research that is blinded, involves multiple sites, targets vulnerable subjects, or employs high-risk interventions. The IRB has the authority to require a DSMB/DMC as a condition for approval of research where it determines that such monitoring is needed.

In lieu of requiring that safety monitoring information be submitted directly to the IRB, the IRB may rely on a current statement from a duly constituted DSMB/DMC indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, and has determined that it continuation of the research is justified.

XIII. **Privacy and Confidentiality Provisions Are Adequate.** In order to approve research, the IRB must determine that, where appropriate, there are adequate
provisions to protect the privacy of subjects and the confidentiality of data.

It is important to be sure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individual. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research.

It also is important to protect individually identifiable private information once it has been collected in order to prevent a breach of confidentiality that potentially could harm subjects. When information linked to individuals will be recorded as part of the research design, the IRB requires that adequate precautions will be taken to safeguard the confidentiality of the information.

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

In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that likely would result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

A. **Certificates of Confidentiality.** Where research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes.

In such situations, the IRB may require that an investigator obtain a DHHS Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DHHS or FDA for audit purposes. Consequently, the IRB will require that these conditions for release be stated clearly and explicitly in the informed consent document.
Information concerning Certificates of Confidentiality can be obtained from any of the following websites:

http://www.nimh.nih.gov/research/confident.cfm
http://www.niaaa.nih.gov/extramural/confidential.htm
http://www.nida.nih.gov/funding/confidentialityfaq.html
http://www.hrsa.gov/quality/certconf.htm
http://www.nhlbi.nih.gov/funding/policies/certsinfo.htm

XIV. Additional Safeguards for Vulnerable Subjects Are Appropriate. In order to approve research, the IRB must determine that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with mental disabilities, or economically or educationally disadvantaged persons. Details about protections for vulnerable subjects are provided in Chapters 9 & 10.

Should the IRB find that they regularly review research involving such vulnerable subjects, the IRB will include among its reviewers persons who are knowledgeable about and experienced in working with these vulnerable subjects.

XV. Research Involving Data Sets and Repositories. When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information. Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

A. In making this determination, the IRB will first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

B. If this is not the case, then the IRB will consider whether it is permissible to waive the usual informed consent requirements in accordance with 45 CFR 46.116(d). Many times, a waiver of consent will be appropriate.

C. In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses “anonymized” data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a
manner that neither the investigator nor the source maintaining the data set can re-establish subjects’ identities.

D. An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by OHRP (see below and refer to Guidance on this topic on the OHRP Website).

XVI. Research Utilizing Data or Tissue Repositories. Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

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

Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, storage, secure maintenance, and sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is not required. (Refer to Guidance on this topic on the OHRP Website and in Appendix V.)

Typically, these parameters involve formal, written agreements stipulating these conditions:

A. The repository will not release any identifiers to the investigator;

B. The investigator will not attempt to recreate identifiers, identify subjects, or contact subjects;

C. The investigator will use the data only for the purposes and research specified; and

D. The investigator will comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

XVII. Epidemiology Research. Epidemiology research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiology research may also combine historical research with survey and interview research.
Epidemiology studies often present significant problems regarding both privacy and confidentiality.

A. The IRB will first consider privacy issues, and must be satisfied that the research does not constitute an unwarranted invasion of the subjects’ privacy. In doing so, the IRB will seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

B. Once the IRB’s privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB will seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

C. Because epidemiology research typically requires very large numbers of subjects, epidemiology investigators almost always request that the IRB waive the usual requirements for informed consent. In order to approve such a waiver in epidemiology research, the IRB must find and document that the first three criteria at 45 CFR 46.116(d) for a waiver of informed consent have been met; specifically that (a) the research presents no more than minimal risk to subjects; (b) the waiver will not adversely affect the rights and welfare of the subjects; and (c) the research could not practically be carried out without the waiver. The fourth requirement (“whenever appropriate, the subjects will be provided with additional pertinent information after participation”) usually does not apply.

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

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

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB will expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained. Genetics Research at HSS is further detailed in Chapter 23.
XIX. **Family History Research.** Family history research is a common technique used in Bio-Social and Bio-Behavioral Research. Family history research typically involves obtaining information from one family member (called a proband) about other family members.

A. It is important to recognize the Federal regulations and the Common Rule include in the definition of human subject a living individual about whom an investigator obtains “identifiable private information.”

B. Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them.

C. The IRB must determine whether family members are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 45 CFR 46.116(d).

XX. **Compliance with All Applicable Laws.** All human subject research conducted at HSS or by its employees or agents must comply with all applicable laws and regulations of the United States and the State of New York, as well as with any local requirements.