Regulatory “Cheat Sheets” for Easy Reference

Criteria for IRB approval of research [DHHS - 45 CFR 46.111; FDA - 21 CFR 56.111]

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied

(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 disabled 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 §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.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Basic elements of informed consent [DHHS - 45 CFR 46.116(a); FDA - 21 CFR 50.25(a)]

(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; and

(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.

Additional Elements [DHHS - 45 CFR 46.116(b); FDA - 21 CFR 50.25(b)]

When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) 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) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) 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; and

(6) The approximate number of subjects involved in the study.

Alteration or Waiver of Consent [DHHS - 45 CFR 46.116(d); not for FDA research]

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
(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.

Waiver of Requirement for Signed Consent [DHHS - 45 CFR 46.117(c)]

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That 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. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That 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.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Documentation of Consent in FDA-regulated Research [FDA - 21 CFR 56.109]

(c) An IRB shall require documentation of informed consent in accordance with 21 CFR 50.27 (requires subject or LAR to sign consent form and be given a copy, allows for short form) except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in 50.24 of this chapter for an exception from informed consent for emergency research are met. *(NOTE that UNC does not currently allow this kind of research)*

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

Additional Protections for PRISONERS

Permitted Categories of Research Involving Prisoners [DHHS - 45 CFR 46:306(a)(2)]

(i) Study of 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.

(ii) Study 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.

(iii) 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) provided that the study may proceed only after the Secretary (through OHRP) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of his intent to approve such research.

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. *(NOTE restrictions on control groups which may not benefit)*…or…

An additional fifth category of permissible research provided by HHS Secretarial waiver for certain epidemiological research conducted or supported by HHS. The research must have as its sole purpose (i) to describe the prevalence or incidence of a disease by identifying all cases, or (ii) to study potential risk factor associations for a disease.

The IRB must review the study and approve it only if it finds that [45 CFR 46:305(a)]:

(1) The research represents one of the categories listed above;

(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 Board 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 Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Additional Protections for CHILDREN

Permitted Categories of Research Involving Children [DHHS and FDA regs both cited]

45 CFR 46.404 and 21 CFR 50.51 Research not involving greater than minimal risk. Permission of one parent or guardian is sufficient.

45 CFR 46.405 and 21 CFR 50.52 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. Permission of one parent or guardian is sufficient.

45 CFR 46.406 and 21CFR 50.53 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. Both parents must give permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child.

45 CFR 46.407 and 21 CFR 50.54 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. Both parents must give permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent/guardian has legal responsibility for the care and custody of the child.

Assent and Parental Permission

[DHHS - 45 CFR 46.408(a); FDA - 21 CFR 50.55 (a - d)] The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

[DHHS - 45 CFR 46.408(c); NOT in FDA research] Parental permission may be waived if, in addition to the general provisions for waiver, the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

Wards

[DHHS - 45 CFR 46.409; FDA - 21 CFR 50.56] Children who are wards of the state or other agency, institution or entity can be included in research under (DHHS - 45 CFR 46.407 or 46.407; FDA - 21 CFR 50.53 or 50.54) only if the research is: (1) related to their status as wards or (2) conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards. Also enrollment of a child who is a ward of the State, including foster children, requires appointment of an IRB-approved advocate for the child. This advocate must be in addition to any other individual acting on behalf of the child as foster parent or guardian. Investigators should contact the IRB prior to enrolling children who are wards.

Additional Protections for PREGNANT WOMEN, FETUSES, NEONATES

[DHHS - 45 CFR 46.204] Pregnant women or fetuses may be involved in research if all of the following conditions are met:

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

(b) The risk to the fetus is 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 any other means;

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

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D;

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

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

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

[DHHS - 45 CFR 46.205] (a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

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

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

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

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

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that: (i) 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 (ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;
(2) The research will not terminate the heartbeat or respiration of the neonate;
(3) There will be no added risk to the neonate resulting from the research;
(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D.

[DHHS - 45 CFR 46.206] Research involving, after delivery, the placenta, dead fetus or fetal material

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

[DHHS - 45 CFR 46.207] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements above [46.204 or 46.205] only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and
(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of Pregnant women [46.204] as applicable; or

(2) The following: (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; (ii) The research will be conducted in accord with sound ethical principles; and (iii) Informed consent will be obtained in accord with the informed consent provisions of 45 CFR 46 subpart A (Basic HHS Policy for Protection of Human Research Subjects) and other applicable subparts of 45 CFR 26 subpart B.

MEDICAL DEVICES [FDA regulated]

Significant Risk Device

Under 21 CFR 812.3(m), an SR device means an investigational device that:
- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Non-Significant Risk Device

An NSR device is an investigational device that does not meet the definition of a significant risk device. If an IRB finds that an investigational medical device study poses a NSR, the sponsor does not need to submit an IDE to FDA before starting the study. If the IRB determines that the proposed study is an NSR study, the IRB may proceed to review the study under 21 CFR 56.109 and 21 CFR 56.111. FDA considers an NSR device study to have an approved IDE after IRB approval and when sponsors meet the abbreviated requirements at 21 CFR 812.2(b). Consequently, in most cases, FDA is not aware of non-significant risk device studies.

As stated above, if FDA has already made the risk determination, the IRB does not need to duplicate this effort. If, however, FDA has not made the risk determination or the IRB disagrees with the NSR determination made by a sponsor, then the IRB must notify the investigator and, where appropriate, the sponsor, that the study involves a significant risk device (21 CFR 812.66). If a sponsor or an IRB needs help in making the SR/NSR determination, it may ask for a written determination from FDA. The IRB should consider the following in determining whether a device study poses a SR or NSR:

- the sponsor's description of why the study is not SR
- whether the proposed NSR research study meets the definition of "significant risk" (see above)
- the proposed use of the device as well as any protocol related procedures and tests, not just the device (test article) alone. (This process is different from the IRB review process found at 21 CFR 56.111(a)(2)).)
- additional information from the sponsor, if needed.

Exempt Device Studies

In accordance with 21 CFR 812.2(b), sponsors and investigators of certain studies are exempt from the requirements of 21 CFR Part 812, with the exception of §812.119 (disqualification of a clinical investigator). Examples of exempt studies are consumer preference testing, testing of a device modification, or testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data, or put subjects at risk. Studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling are exempt from Part 812. Note: Studies of a cleared device *for a new use* must comply with the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations. Similarly, studies of a PMA approved device are exempt from the IDE requirements if the device is being studied for the indications in the approved labeling.

In addition, diagnostic device studies (e.g., *in vitro* diagnostic studies) are exempt from the requirements of 21 CFR Part 812 under certain circumstances. The study is exempt as long as the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. 21 CFR 812.2(c)(3).

Humanitarian Use Device (HUD)
An HUD is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the U.S. per year.

A **Humanitarian Device Exemption (HDE**) is similar to a premarket approval (PMA) application, but is exempt from effectiveness requirements. FDA approval of an HDE authorizes marketing of an HUD, subject to certain profit and use restrictions. Per FDA guidelines, "an HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose." The HDE signifies that FDA has determined that the device is probably effective and reasonably safe; the IRB need not make this determination. Importantly, **use of the HUD is not research.** However, the HDE holder is responsible for ensuring that such use has been approved by an IRB. IRB responsibilities for HUDs/HDEs include:

Initial review:

- Initial IRB approval should be performed at a convened IRB meeting. However, a **formal protocol or IRB application is not required**. The IRB should request a copy of the FDA HDE approval order, description of the device, product labeling, relevant publications and a summary of any screening or follow-up procedures.
- The IRB should ensure that the HUD is being used in accordance with the approved HDE and that the physician using the device is qualified to do so.
- Federal regulations **do not require the use of a consent document;** the IRB will evaluate the need for one and may determine that one is not necessary.
- The physician may collect safety and efficacy data as long as collected in accordance with the approved HDE.
- The IRB does not need to review and approve individual uses of an HUD, but rather the IRB may approve use of the device as it sees fit. That is, the IRB may approve use of the HUD without any further restrictions, under a defined protocol, or on a case-by-case basis.

Continuing review:

- IRBs may approve the use of the device for a period of time, not to exceed one year.
- Continuing review may be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that full board review should be performed.
- The IRB should ensure that the physician reports to the HDE holder/FDA and IRB, whenever a HUD may have caused death or serious injury or has malfunctioned.

Exemptions from Investigational New Drug (IND) Application [FDA - 21 CFR 312.2(b)]

(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.