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Washington University in St. Louis IRB meeting guide

Human Research Protection Office, Washington University School of Medicine in St. Louis

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IRB MEETING GUIDE

Washington University in St. Louis

CRITERIA FOR THE APPROVAL OF RESEARCH (45 CFR 46.111/21 CFR 56.111)

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 (See Consent Elements).

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §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.

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.

The Mission of the Washington University in St. Louis Institutional Review Boards is to protect the rights and welfare of human subjects.

The first ethical review of research involving human subjects at Washington University in St. Louis Medical School began with a small committee of physicians and community volunteers in 1969. The National Research Act in 1974 formalized the review of human subjects research, which led to the Belmont Report in 1978 and the federal regulations that guide the review of human subjects research in 1981.

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Washington University in St. Louis has one of the longest standing traditions of ethical review of research in the US, which predates any federal mandate or guidance for Institutional Review Boards.

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As a member of the WU IRB, you are part of this great heritage that has been built on time volunteered by many scientist, physicians, administrators, and community members. Your contribution is a vital element of the conduct of ethical research, but by participating in the IRB you are also partnering with investigators in their effort to contribute to the advancement of science and knowledge.



CONFLICT OF INTEREST POLICY

IRB Reviewers that have a conflict of interest, potential or otherwise, may only remain in the meeting to answer questions and must leave prior to the discussion and vote.

A **financial conflict of interest** exists whenever a reviewer, (including HRPO staff or consultant) or his/her immediate family (his/her spouse or dependent children):

1. has a financial interest in the research whose value cannot be readily determined;
2. has ownership interest, stock options, or other financial interests related to the research
UNLESS all four of the following criteria are met:
 - a. does not exceed \$10,000 when aggregated for the immediate family;
 - b. is publicly traded on a stock exchange;
 - c. no arrangement has been entered into where the value of the ownership interests will be affected by the outcome of the research; AND
 - d. does not exceed 5% interest in any one single entity when aggregated for the immediate family.
3. has a significant financial interest with the sponsor of the study, the supporting organization, or the company that owns or licenses the technology being studied;
4. has received or will receive any compensation whose value may be affected by the outcome of the study;
5. has a proprietary interest in the research (property or other financial interest in the research including, but not limited to, a patent, trademark, copyright or licensing agreement);
6. has received payments from the sponsor that exceed \$10,000 per year;
7. is an executive or director of the agency/company sponsoring the research; or
8. any other situations defined by WU Conflict of Interest policies.

A **non-financial conflict of interest** exists whenever a reviewer, (including HRPO staff or consultants) or his/her immediate family (his/her spouse or dependent children) is:

1. the protocol director, or other member of the research team;
2. listed on the FDA 1572 form or otherwise involved in the conduct of the study. (A conflict of interest does not exist if the reviewer is only providing a commercial service such as dispensing study medication or performing a blood draw);
3. related to any member of the study team;
4. the faculty advisor of the PI;
5. identified as "key personnel" on a funding mechanism that supports the research project; or
6. any other situation where the reviewer believes that another interest conflicts with his/her ability to deliberate objectively on a protocol.

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Tab	Content	Source/Regulatory Document Referenced
Belmont Report	<i>Belmont Report Summary</i>	Federal Register-1979 Apr 18;44(76): 23192-7
Children	<i>Children in Research</i>	45 CFR 46 Subpart D; SOP VIII.C
CoC	<i>Certificate of Confidentiality</i>	http://grants.nih.gov/grants/policy/coc
Consent Elements	<i>Elements and Documentation of Consent</i>	45 CFR 46.116; 45 CFR 46.117; SOP VII.A-C
Waivers of Consent	<i>Waivers of Consent</i>	45 CFR 46.116(d); 45 CFR 46.117(c)
Waivers of HIPAA Auth.	<i>Waivers of HIPAA Authorization</i>	45 CFR 160, 164
CR	<i>Continuing Review Criteria</i>	SOP III.A.3
DSMB	<i>Data and Safety Monitoring</i>	
Decisionally Impaired	<i>Decisionally Impaired Participants</i>	SOP VIII.D
Devices: IDE, HUD	<i>Use of Devices in Research</i>	FDA Guidance: Frequently Asked Questions About Medical Devices
Devices: SR or NSR	<i>Risks of Devices in Research</i>	FDA Guidance Sheet: Significant Risk and Nonsignificant Risk Medical Device Studies
Drugs: IND	<i>Use of Drugs in Research</i>	FDA Guidance Sheet: IND Exempt/IND Exempt Oncologicals
Motions and Voting	<i>IRB Meeting Guidance</i>	OHRP: Guidance on IRB Approval of Research with Conditions
Pregnant and Neonates	<i>Pregnant and Neonate Populations in Research</i>	45 CFR 46 Subpart B
Prisoners	<i>Prisoner Populations in Research</i>	45 CFR 46 Subpart C
Privacy and Confidentiality	<i>Issues related to Privacy/Conf.</i>	
Abbreviations	<i>Definitions of Key Abbreviations</i>	

**THE BELMONT REPORT -
SUMMARY OF ETHICAL PRINCIPLES FOR THE PARTICIPATION OF HUMAN SUBJECTS IN RESEARCH**

Basic Ethical Principles

1

Respect for Persons. Respect for persons incorporates at least two ethical convictions:

- **Individuals should be treated as autonomous agents. There is an ethical requirement to acknowledge autonomy.**
- **Persons with diminished autonomy are entitled to protection. There is an ethical requirement to protect those with diminished autonomy.**

2

Beneficence. Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Two general rules have been formulated as complementary expressions of beneficent actions in this sense:

- **Do not harm.**
- **The research process must maximize possible benefits and minimize possible harms.**

3

Justice. Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of “fairness in distribution” or “what is deserved.” An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly.

- **The selection of research subjects needs to be scrutinized to determine whether some classes are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied.**
- **Whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.**

CHILDREN IN RESEARCH

45 CFR 46.404 (21 CFR 50.51) - Research not involving greater than minimal risk.

- No greater than minimal risk to children is presented. (Minimal risk means that the probability and magnitude of the 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 exams or tests.)
- The IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 46.408.

45 CFR 46.405 (21 CFR 50.52) - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

- More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:
 - a) The risk is justified by the anticipated benefit to the subjects;
 - b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches;
 - c) Adequate provisions are made for soliciting the assent of the children and permission of the parents or guardians, as set forth in 46.408.

45 CFR 46.406 (21 CFR 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.

- More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:
 - a) The risk represents a *minor* increase over minimal risk;
 - b) 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;
 - c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
 - d) Adequate provisions are made for soliciting the assent of the children and permission of the parents or guardians, as set forth in 46.408.

45 CFR 46.407 (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.

- Research that the IRB does not believe meets the requirement of 46.404, 46.405, or 46.406 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 children; and
 - b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment has determined either:
 - 1) that the research in fact satisfies the conditions of 404, 405, or 406, 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 children adequate; ii) the research will be conducted in accordance with sound ethical principles; iii) adequate provisions are made for soliciting the assent of children and the permission of both parents or guardians as set forth in 46.408.

II. Requirements for Permission by Parents/Guardians and for Assent by Children (45 CFR 46.408).

- a) **Children:** In addition to the determinations required under other applicable sections of this subpart, 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. The IRB shall take into account: *the ages, the maturity, and the psychological state of children involved.*
- This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate.
 - If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.
 - Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 46.116 of Subpart A. (*Refer to the Consent Elements and Waivers sections.*)
- b) **Parents/Guardians:** In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. (*Refer to the Consent and Waivers of Consent section.*)
- Where parental permission is to be obtained, the IRB may find that the permission of *one parent is sufficient* for research to be conducted under **46.404** or **46.405**.
 - Where research is covered by **46.406** and **46.407** and permission is to be obtained from parents, *both parents must give their permission* unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care and custody of the child.
- c) In addition to the provisions for waiver contained in 46.116 of subpart A, if 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), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, 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.
- d) Permission by parents or guardians shall be documented in accordance with and to the extent required by 46.117 of subpart A.
- e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

III. Wards of the State (45 CFR 46.409)

- a)** Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 46.406 or 46.407 only if such 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.

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

CERTIFICATES OF CONFIDENTIALITY

Certificates of Confidentiality (CoCs) are issued by the Food and Drug Administration (FDA) and National Institutes of Health (NIH). A CoC may add additional protection for studies where an investigator will be collecting sensitive and identifiable information that “if disclosed could have adverse consequences for subjects or damage their financial standing, employability, insurability, or reputation.”

- I. A CoC specifically prevents the disclosure of identifiers that would link a participant to research data. A CoC allows an investigator to refuse disclosing identifiable information collected during research in any civil, criminal, or legislative proceeding at the local, state, and federal level.
- II. A CoC may help promote enrollment in studies by providing additional protections with regard to the confidentiality of a subject’s participation in the research.
- III. A CoC does not protect against:
 - Voluntary disclosure by the investigator of things like child abuse, reportable participant threat to self or others, or any additional disclosure that has been identified in the consent form.
 - Voluntary compliance by the investigator with state law regarding the reporting of communicable diseases.
 - Voluntary release of research data to DHHS or FDA as required for audits or program evaluations.
 - Voluntary release by the participants themselves.
 - Mandated release of data (such as by subpoena if the fact that the subject is a part of the research study is known by some other means.
- IV. A CoC may also be an additional way to minimize risks in studies involving:
 - Sensitive information on the psychological health of participants.
 - Sensitive information on drug abuse or other illegal behaviors.
 - Sensitive information on participants’ sexual preferences or behaviors.
 - Genetic or genomic data.

ELEMENTS OF CONSENT

I. **Basic Elements of Informed Consent (45 CFR 46.116(a)):**

In seeking informed consent the following information shall be provided to each subject:

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.

II. **Additional Elements of Informed Consent (45 CFR 46.116(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 participant is or becomes pregnant) which are currently unforeseeable;
2. The anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the participant'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 participants involved in the study.

Note: Informed consent may also require reference to Missouri State Law (RSMo Chapters 565.188 (mandatory reporting of elder abuse) and 210.115 (mandatory reporting of child abuse)).

III. Documentation of Consent (45 CFR 46.117)

- a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.
- b) The consent form may be either of the following:
 - 1) A written consent document that contains the elements of informed consent required by 46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate time to read the consent document before it is signed; or
 - 2) A "short form" written consent document stating that the elements of informed consent required by 46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used:
 - There shall be a witness to the oral presentation.
 - Also, the IRB shall approve a written summary of what is to be said to the subject or the representative.
 - Only the short form itself is to be signed by the subject or the representative.
 - However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign and copy of the summary.
 - A copy of the summary shall be given to the subject or the representative, in addition to a copy of the form.
- c) The 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 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 provides 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.

WAIVERS OF CONSENT

I. **Waiver or Alteration of Consent (45 CFR 46.116(d)):**

*A Waiver or Alteration of Consent can only be approved for research that is **not** subject to FDA regulations. FDA does permit the Waiver of Consent in minimal risk studies.*

The 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.

II. **Waiver of Documentation of Consent (45 CFR 46.117(c)):**

*If research is subject to FDA regulations a Waiver of Documentation of Consent must qualify under criterion 2 below. Criterion 1 is **not** allowed under FDA regulations.*

The 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 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 provides 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.

WAIVER OF HIPAA AUTHORIZATION

I. HIPAA Authorization

HIPAA requires the signature of an individual to authorize the use of their PHI for research purposes. As this is the case, if the IRB approves a Waiver of Consent or Waiver of Documentation of Consent, it will also approve a Waiver of HIPAA Authorization, as no signature will be obtained. The HIPAA regulations do not have a regulation analogous to the Waiver of Documentation allowed under DHHS regulation. Therefore, even if all of the authorization information is provided to a participant, if the authorization is not signed, all criteria below must be met to grant a partial waiver. (*See diagram below.*)

- **Full or Partial Waiver of Authorization:** The HIPAA Privacy Rule (45 CFR 160, 164) requires investigators to obtain a signed and dated authorization from research subjects to use their protected health information for research purposes. If certain conditions are met, the IRB may waive the requirement for investigators to obtain an altered authorization (for example one lacking a signature and/or dated authorization from subjects.)

- The IRB or privacy board has determined that the alteration or waiver, in whole or in part, of authorization satisfies the following criteria (Privacy Rule - 164.512(i)(2)):

- The use or disclosure of the requested information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
 - 1) An adequate plan to protect the identifiers from improper use and disclosure.
 - 2) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
 - 3) Adequate written assurances that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule;
 - 4) The research could not practicably be conducted without the waiver or alteration; and
 - 5) The research could not practicably be conducted without access to and use of the requested information.

II. Diagram of IRB/Privacy Board Responsibilities:

	HIPAA Privacy Rule	DHHS – 45 CFR 46	FDA – 21 CFR 50, 56
Required Permission for Research	Authorization to use of PHI for research.	Consent to use of identifiable information for research.	Consent to use of identifiable information for research.
IRB/Privacy Board Responsibilities	The covered entity must obtain Authorization for research use or disclosure of PHI unless a regulatory permission applies. While acting as the Privacy Board, the IRB can grant waivers to this authorization	The IRB must review and approve the consent form and process for proposed research. While acting as the IRB, the IRB can grant waivers or alterations to this process.	The IRB must review and approve the consent form and process for proposed research. While acting as the IRB, the IRB can only grant waivers in specific circumstances.

CONTINUING REVIEW

At the time of initial review and at continuing review, the committee will make a determination regarding the frequency of review of the research protocols. All protocols will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year for the duration of the research. In some circumstances, a shorter review interval (e.g. biannually, quarterly, or after accrual of a specific number of participants) may be required. This may be preferable when approving, for example:

- Investigational therapies that have potential for significance adverse events.
- Studies that involve vulnerable populations or significant privacy risks.
- Studies that have exhibited serious or ongoing compliance issues.

The Full Board may determine during any convened rule that a study meets the criteria below for future continuing review via expedited reviews:

- All continuing reviews that meet the criteria required in Category 9 of the list of research activities which may be reviewed through expedited review procedures will be reviewed by qualified members who have been designated by the Executive Chair to conduct expedited review. All expedited reviews of protocols will be reported to the Full Board. (45 CFR 46.110).
- *Category 9:* Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (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.

DATA AND SAFETY MONITORING

There is no single model that is optimal for all settings nor is there a consensus about an optimal model. Each monitoring model has its advantages and disadvantages. Monitoring can range from the PI or research team looking at the data for trends to an outside monitor checking the study for safety or a group of individuals who are affiliated with the study reviewing safety reports to an independent data monitoring committee. All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors, and investigators.

I. Role of a Data and Safety Monitoring Plan:

- On occasion, if it is warranted, a committee may receive an individual event to review. Otherwise, committees are given data summaries and/or summaries of adverse events. Quite often these data summaries are given to the committee once a substantial portion of the study has been conducted. Therefore, data monitoring committees cannot provide additional protections for a specific site. Nor are they recommended for trials that will be short in duration.
- Meeting frequency depends on the needs of the trial. There are no mandates that the committee meet at least annually.
- Members of independent data monitoring committees are generally paid by the sponsor.

II. Reviewing a Study With a Data and Safety Monitoring Plan:

- Remember that the primary mandate of the IRB committee is to evaluate a study to ensure that risks are reasonable in relation to benefits.
- A data monitoring committee may not necessarily increase the safety level of the study, if the study is relatively short in duration or if the risks of a treatment or procedure are relatively low or well-established.
- The IRB committee needs to decide whether the data and safety monitoring plan established by the sponsor or investigator is adequate based on the proposed outcomes in the study, the level of risks, the size and duration of the study, the fragility or vulnerability of the population(s) being studied, and the existing data.

DECISIONALLY IMPAIRED PARTICIPANTS

In addition to the criteria for approval (45 CFR 46.111), the IRB will take into consideration the following additional points when reviewing research involving adults with impaired decision-making capacity:

- *How the investigator plans to assess impairment at the time of initial consent and throughout the course of the study.*
- *How the investigator plans to assent participants that are decisionally impaired.*
- *Who meets the DHHS and FDA definition of “legally authorized representative” under the applicable law of the jurisdiction in which the research will be conducted.*
- *How the investigator will consent the legally authorized information and assure that they understand their role in acting on behalf of the potential participant.*

- I. Assessing Decisional Impairment:** There are no well-established, standardized measures for determining competency to consent to research. Therefore, assessment should be done on an individual basis and should determine the ability of the potential subject to:
 - Understand the nature of the research, its risk, benefits, and of his or her participation.
 - Appreciate the consequences of the participation.
 - Show the ability to consider alternatives, including the option not to participate.
 - Show the ability to make a reasoned choice.
 - All of these subject abilities may not be necessary for a given research protocol; greater ability is required for protocols with greater risk.
- II. Consenting Decisionally Impaired Participants:** If the potential subject is not sufficiently competent, informed consent should be obtained from his or her legally authorized representative, and assent should be obtained from the subject.
- III. To approve a study that proposes enrollment of decisionally impaired individuals, the IRB needs to additionally consider:**
 - The risk/benefit ratio of the study, as research with potential benefit to the subject is more readily approvable with this population than research with little or no potential benefit.
 - The ongoing nature of consent, as special requirements exist for long-term studies during which there may be a reasonable presumption of declining capacity in the potential research subject.
 - Whether this is the only population that can potentially answer the research question, or whether a different population that would be competent to consent for themselves could be enrolled.

INVESTIGATIONAL DEVICE EXEMPTIONS

A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (21 U.S.C. 321(h)):

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and
- which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

- I. A device is considered *investigational* when it is used as part of a clinical investigation. A clinical investigation is an experiment involving one or more human subjects that determines the safety and effectiveness of a device.

II. Devices Subject to IDE Regulations

The FDA may make an SR or NSR determination. The IRB may make an NSR determination. If the IRB thinks a device may be SR, then the investigator must submit it to the FDA for further review.

- **Significant Risk Devices (21 CFR 812.3(m))**
 - i. Subject to Full IDE Reporting and Monitoring Requirements
 - ii. Definition: *A device that:*
 1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
 2. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety and welfare of a subject;
 3. 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
 4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- **Non-Significant Risk Devices**
 - i. Subject to Abbreviated Reporting and Monitoring IDE Requirements
 - ii. Definition: *Does not meet the definition of "Significant Risk."*

III. Devices Not Subject to IDE Regulations (21 CFR 812.2(c))

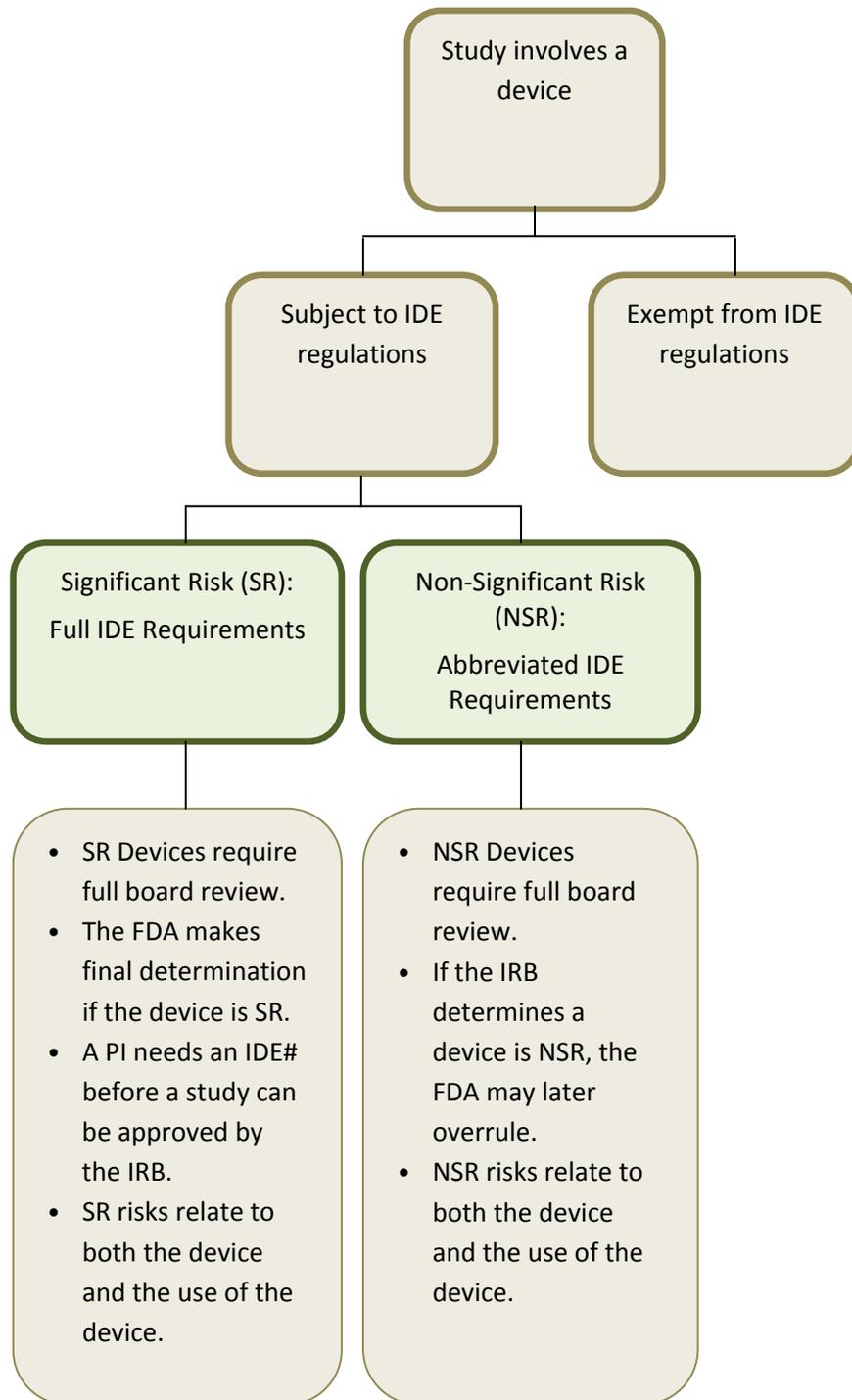
The IRB or FDA may determine that a study is exempt from the IDE regulations in the case of:

- **Diagnostic Devices, if:**
 - i. It is noninvasive,
 - ii. Does not require a sampling procedure that presents significant risk,
 - iii. Does not by design or intention introduce energy into the subject, and
 - iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established product or procedure.

- **Consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if :**
 - i. The testing is not for the purpose of determining the safety and effectiveness of the device or modification, and
 - ii. The testing does not place participants at risk.

- **Basic Physiological Research, if:**
 - i. The device is used to test a physiological principle, and is simple being used to collect samples or facilitate research.
 - ii. The safety and effectiveness of the device is not being investigated.
 - iii. There is no intention to develop the device for marketing.

INVESTIGATIONAL DEVICE EXEMPTION - FLOWCHART



HUMANITARIAN DEVICE EXPEMPTION

A Humanitarian Use Device (HUD) is a device designed to treat or diagnose a condition that affects fewer than 4,000 individuals per year, and no other device is comparable.

- I. Humanitarian Device Exemption (HDE) is an approval mechanism the FDA uses to allow the marketing of HUDs. The FDA will grant an HDE to a device in this case even though it has not been tested for efficacy because a full clinical trial would not be feasible. The HDE approval is based on demonstration of probable benefit from the device based on bench or animal testing and summaries of clinical experience (21 CFR 814 Subpart H).
- II. There are two types of HUD reviews performed by the IRB:
 - IRB approval is required before a HUD is used to treat or diagnose patients.
 - An IDE may be required for the clinical investigation of a HUD, whether the HUD is being studied for its HDE-approved indications or for a different indication. Even if the IRB has approved the use of a HUD in a clinical setting, that does not mean that the IRB has approved investigational use of the HUD for the collection of safety and effectiveness data.

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Frequently Asked Questions About Medical Devices

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<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Center for Biologics Evaluation and Research**

January 2006

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Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors¹ Frequently Asked Questions About Medical Devices

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist clinical investigators and institutional review boards (IRBs) by answering common questions FDA receives concerning medical devices. This document supersedes *Medical Devices, Frequently Asked Questions about IRB Review of Medical Devices*, and *Emergency Use of Unapproved Medical Devices* (September 1998) Office of Health Affairs, Food and Drug Administration. This document was revised to make it consistent with the Agency's good guidance practices regulations (21 CFR 10.115).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. FREQUENTLY ASKED QUESTIONS ABOUT MEDICAL DEVICES

¹ This guidance document was developed by the Good Clinical Practice Program in coordination with the Agency Centers. This guidance document does not address medical devices subject to licensure as a biological product. Please direct questions concerning those devices to the Center for Biologics Evaluation and Research.

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1. What is a medical device?

A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

2. How does FDA classify medical devices?

In accordance with the Federal Food, Drug, and Cosmetic Act, FDA places all medical devices into one of three regulatory classes based on the level of control necessary to ensure safety and effectiveness of the device. Classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in determining the class to which it is assigned.

Devices in all three classes are subject to general controls which require, in part, that companies: (1) register their establishments and list the medical devices they market with FDA; (2) manufacture their devices in accordance with Good Manufacturing Practices; and (3) label their devices in accordance with labeling regulations.

Class I devices are subject only to general controls. They typically present the lowest potential for harm and are simpler in design than Class II or Class III devices. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Class II devices are those for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness. In addition to complying with general controls, Class II devices are also subject to special controls identified by the agency, which may include special labeling requirements, performance standards and postmarket surveillance. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

Class III devices generally are those for which insufficient information exists to determine that general or special controls are sufficient to provide a reasonable assurance of safety and effectiveness. Examples of Class III devices include replacement heart valves, silicone gel-filled breast implants, and implanted cerebellar stimulators.

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3. What are examples of medical devices?

Examples of medical devices include surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. A longer list of examples of medical devices is in the FDA Information Sheet Guidance, “Significant Risk vs. Non-Significant Risk Devices.”

Medical devices also include diagnostic products. Examples of diagnostics include in vitro diagnostic reagents and test kits such as pregnancy test kits, and imaging systems such as magnetic resonance imaging (MRI).

4. What is a premarket notification (510(k)) submission?

A premarket notification, or 510(k), is submitted to FDA before a manufacturer proposes to market a medical device. If FDA agrees the new device is substantially equivalent to a legally marketed device for which premarket approval is not required, the manufacturer may market it immediately. FDA does not require clinical data in most 510(k)s. However, if clinical data are necessary to demonstrate substantial equivalence, the clinical study must comply with the IDE, IRB, and human subject protection (informed consent and additional safeguards for children in research) regulations. See section 520(g) of the act and 21 CFR Parts 812, 56 and 50.

5. What is a premarket approval (PMA) application?

A premarket approval (PMA) application is the most stringent type of device marketing application for medical devices. FDA approves a PMA if it determines that the application contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s).

6. Where can I find more information about 510(k)s and PMAs?

Additional information is available about these programs on the Center for Devices and Radiological Health’s website at: www.fda.gov/cdrh/devadvice/.

7. What is a 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 United States per year. The Office of Orphan Products Development (OOPD) determines if a device meets specific requirements, including scientific rationale and population prevalence, for designation as a HUD.

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8. What is a humanitarian device exemption (HDE) application?

A Humanitarian Device Exemption (HDE) application is similar to a PMA, but because a HUD is exempt from the effectiveness requirements of a PMA, 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. However, the HDE must contain sufficient information for FDA to determine that the probable benefit to health outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Section 520(m)(2)(C). An approved HDE authorizes marketing of an HUD.

Under the statute, once the HDE is approved, the HDE holder is responsible for ensuring that the approved HUD is only administered at institutions that have an IRB constituted and acting pursuant to 21 CFR 56, including conducting continuing review of the use of the HUD. In addition, an HUD should be administered only if such use has been approved by the Institutional Review Board (IRB) located at the facility, or by a similarly constituted IRB that has agreed to oversee such use and to which the local IRB has deferred in a letter to the HDE holder. An HDE holder may wish to ensure that this happens by not shipping the HUD to the facility until it has received confirmation of IRB approval.

NOTE: HUDs should not be used until AFTER the HDE applicant obtains approval of the HDE from FDA and the IRB approves its use. IRBs should ensure that HDE approval has been granted before approving the device for use at their institution.

9. What are the responsibilities of the IRBs regarding HDEs?

Initial review:

Initial IRB approval should be performed at a convened IRB meeting. 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 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. 21 CFR 56.109(f). In some higher risk cases, IRBs have approved HUDs for a specific number of patients and have required a summary report before approving the use in additional patients. Continuing review should follow the requirements found at 21 CFR 56, and 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 agency believes that the expedited review procedures are appropriate for continuing review since the initial review would have been performed by the full board and use of the HUD within its approved labeling does not constitute research.

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10. Is informed consent required when treating/diagnosing a patient with an HUD?

The act and the HDE regulations do not require informed consent. Because an HDE provides for marketing approval, use of the HUD does not constitute research or an investigation which would normally require consent from the study subjects. However, there is nothing in the law or regulations that prohibits a state or institution from requiring prospective informed consent, when feasible. In fact, most HDE holders have developed patient labeling that incorporates information that may be used to assist a patient in making an informed decision about the use of the device. For example, the patient labeling may contain a discussion of the potential risks and benefits of the HUD, as well as any procedures associated with the use of the device. The HUD labeling also states that the device is a humanitarian use device for which effectiveness for the labeled indication has not been demonstrated. See 21 CFR 814.104(b)(4)(ii).

Unless it is an emergency, before an HUD is used off-label, the agency recommends that the HDE holder obtain FDA approval of the use following the compassionate use policy for unapproved devices. (See Chapter III Expanded Access to Unapproved Devices of the “IDE Policies and Procedures Guidance.”²) If FDA approves the compassionate use request, the physician should ensure that the patient protection measures are addressed before the device is used and should devise an appropriate schedule for monitoring the patient. If the situation is life-threatening and there is not time to get FDA approval for the off-label use, FDA recommends that the emergency use procedures outlined in the above referenced guidance be followed.

Sometimes a physician or HDE holder may develop a research protocol designed to collect safety and effectiveness data to support a PMA for the device. In that case, an IDE is not needed if the research is within the approved labeling; however, IRB approval for the investigational study must be obtained before the research may begin. Informed consent must also be obtained from the subjects participating in the study. If the research is for a **new use**, the IDE regulation must be followed. 21 CFR Parts 812, 50, and 56.

11. What statute and regulations apply to medical device clinical investigations?

In accordance with section 520(g) and the regulations, clinical studies of medical devices must comply with FDA’s human subject protection requirements (informed consent and additional safeguards for children in research) (21 CFR Part 50), Institutional Review Board (IRB) requirements (21 CFR Part 56), Investigational Device Exemptions (IDE) requirements (21 CFR Part 812), Financial Disclosure for Clinical Investigators requirements (21 CFR Part 54) regulations, as well as any other applicable regulations, including pertinent regulations at 21 CFR Part 809 (In Vitro Diagnostic Devices For Human Use).

12. What types of device studies do the IDE regulations (21 CFR Part 812) cover?

² This guidance may be found at www.fda.gov/cdrh/ode/idepolicy.html

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There are three types of studies described in the regulations at 21 CFR Part 812: significant risk (SR) device studies, non-significant risk (NSR) device studies, and exempt studies. A brief description of these types of studies follows. Please refer to the FDA Information Sheet Guidance “Significant Risk and Nonsignificant Risk Medical Device Studies” for more detailed information about SR and NSR device studies, the importance of the IRB’s review, the regulatory requirements for these studies, and examples of devices in each category.

A. Significant Risk Device Studies

A significant risk 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 a use in 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. (21 CFR 812.3(m))

Sponsors of investigational SR device studies are required to get an approved IDE from FDA before starting their study. 21 CFR 812.20 (FDA gives each IDE a number - for example #GXX0000, where XX denotes the year of the submission). Sponsors and clinical investigators of these studies must comply with the regulations at 21 CFR Part 812, "Investigational Device Exemptions."

If FDA disapproves an IDE, FDA’s letter will describe the reasons for the disapproval. If the sponsor submits an IDE amendment satisfactorily addressing the issues in FDA’s letter, the agency sends an IDE approval letter to the sponsor. In accordance with the regulations at Part 812, the study may not start until both FDA and the IRB have given their approval.

Note: A conditional approval letter from FDA allows the study to begin if the study is approved by the IRB, but requires the sponsor to provide additional clarifying information in order to obtain full approval for the study.

IRBs do not have to make the SR or NSR determination if FDA has already made the risk determination. Most often, clinical investigators submit SR device investigations for IRB review after the study has already received IDE approval from FDA. IRBs may ensure that SR device investigations have an FDA-approved IDE by asking the clinical investigator to request from the sponsor a copy of FDA’s IDE approval letter.

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An IRB may be asked to review an SR device study before the sponsor receives FDA approval of an IDE submission. Under this circumstance, IRBs should be aware that because it is possible that FDA may not approve the IDE or may request significant changes to the research protocol, the IRB may need to re-evaluate the study after FDA reviews the application. If an IRB approves the significant risk device study before FDA approves the IDE, there may be more of a risk that clinical investigators will mistakenly enroll subjects before the study should be started (i.e, before FDA approves the IDE.)

B. Non-Significant Risk Device Studies

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.³

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.

³ See the guidance memorandum entitled, "Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices" at www.fda.gov/cdrh/ode/blue-ide-d01-1.html

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C. Exempt 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.⁴

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 812.⁵ 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).

13. Are IDE exempt studies subject to the requirements for informed consent and IRB review and approval under Parts 50 and 56?

If an exempt study is being conducted to collect data to support either a clinical investigation or a marketing application, then the study must comply with 21 CFR Part 50 and should comply with 21 CFR Part 56. 21 CFR 50.1(a), 21 CFR 50.20, 21 CFR 56.101(a), 21 CFR 56.103.

14. Does FDA require IRB review and approval of off-label use of a legally marketed device?

No, when a physician uses a legally marketed device outside its labeling to treat a patient and no research is being done, IRB review is not required. Note: Although not required by FDA, an IRB may still decide on its own initiative to review such use. Yes, when the off-label use of a legally marketed device is part of a research study collecting safety and effectiveness data involving human subjects, IRB review and approval is required (21 CFR 812.2(a)).

⁴ See 21 CFR 812.2(c)(4).

⁵ See 21 CFR 812.2(c)(1) and (2).

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For additional information on the off-label use of devices, see the FDA Information Sheet guidance, “ ‘Off-label’ and Investigational Use of Marketed Drugs, Biologics and Medical Devices.”⁶

15. Must an IRB review a study conducted after submission of a (510(k)) to FDA but prior to FDA’s decision on that submission?

Yes. During FDA’s review of the premarket notification submission, the device remains an investigational product. Therefore, the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations apply. The device may not be distributed, except for investigational use, unless FDA clears the device for marketing.

16. Can a physician use an unapproved device in an emergency?

In general, an unapproved medical device may be used only on human subjects when the device is under clinical investigation and when used by investigators participating in a clinical trial. Section 561 of the Act, however, recognizes that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to prevent irreversible morbidity when there exists no other alternative therapy. For investigational devices under an IDE, the IDE regulation permits deviations from the investigational plan without prior approval when necessary to protect the life or physical well-being of a subject in an emergency. (See 21 CFR 812.35(a)). A physician may treat a patient with an unapproved medical device in an emergency situation if he/she concludes that:

- The patient has a life-threatening condition that needs immediate treatment;⁷
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many of the patient protection procedures listed below as possible:

- Informed consent from the patient or a legal representative;
- Clearance from the institution as specified by their policies;

⁶ This guidance can be found at: www.fda.gov/oc/ohrt/irbs/offlabel.html

⁷ FDA considers “life-threatening condition” to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity.

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- Concurrence of the IRB chairperson;
- An assessment from a physician who is not participating in the study; and
- Authorization from the IDE sponsor, if an IDE exists for the device.

While prior approval for shipment or emergency use of the investigational device is not required, the use must be reported to FDA by the IDE sponsor within 5 working days from the time the sponsor learns of the use. 21 CFR 812.35(a)(2) and 812.150(a)(4). The report should contain a summary of the conditions constituting the emergency, patient outcome information, and the patient protection measures that were followed. If no IDE exists, the physician should follow the above procedures and report the emergency use to CDRH or CBER.

For additional information on the procedures physicians and IRBs should follow in an emergency use situation, please see Chapter III Expanded Access to Unapproved Devices of the guidance entitled, "IDE Policies and Procedures."⁸

17. What if the situation is not an emergency? Can a patient with a serious illness or condition have access to an investigational device outside a study?

Yes, FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious or life-threatening condition (hereinafter referred to as "compassionate use"). Unlike emergency use of an unapproved device discussed above, prior FDA approval is needed before compassionate use occurs. Section 561(b) of the act and 21 CFR 812.35. In order to obtain agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. The IDE supplement should include:

- A description of the patient's condition and the circumstances necessitating treatment;
- A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
- An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
- The patient protection measures listed above that will be followed.

⁸ This guidance may be found at: www.fda.gov/cdrh/ode/idepolicy.html

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The patient identified in the supplement should not be treated with the device until FDA approves its use under the proposed circumstances. In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, they should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

Additional information on the procedures physicians and IRBs should follow in compassionate use situations may be found in Chapter III Expanded Access to Unapproved Devices of the guidance entitled, “IDE Policies and Procedures.”⁹

18. What is the definition of a custom device?

To be considered a custom device, the device must meet all of the following criteria, which are described in section 520(b) of the act and at 21 CFR 812.3(b):

- (1) It necessarily deviates from devices generally available or from an applicable performance standard or premarket approval requirement in order to comply with the order of an individual physician or dentist;
- (2) The device is not generally available to, or generally used by, other physicians or dentists;
- (3) It is not generally available in finished form for purchase or for dispensing upon prescription;
- (4) It is not offered for commercial distribution through labeling or advertising; and
- (5) It is intended for use by an individual patient named in the order form of a physician or dentist, and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice (such as a particular operating tool).

19. Does an IRB need to review custom use?

FDA regulations do not require review and approval for custom device use. However, FDA recommends that as many of the patient protection measures listed in paragraph 16 be followed as possible. IRBs should be familiar with the regulatory requirements for custom devices

⁹ This guidance may be found at: www.fda.gov/cdrh/ode/idepolicy.html

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because physicians or institutions may seek information from the IRB about the use of a custom device in patients at their healthcare facility. IRBs may develop procedures for the use of custom devices to ensure that patient protection measures are thoughtfully carried out.

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)**

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**Information Sheet Guidance
For IRBs, Clinical Investigators, and Sponsors¹
Significant Risk and Nonsignificant Risk Medical Device Studies**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide advice to sponsors, clinical investigators, and institutional review boards (IRBs) on how to determine the differences between significant risk and nonsignificant risk medical device studies. This document supersedes *Significant Risk and Nonsignificant Risk Medical Device Studies* (September 1998) Office of Health Affairs, Food and Drug Administration. This document was revised to update the list of examples of significant and nonsignificant risk devices, to clarify the IRB's responsibilities when making the risk determination for investigational medical devices, and to make the guidance consistent with the Agency's good guidance practices regulations (21 CFR 10.115).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

¹ This guidance document was developed by the Good Clinical Practice Program in coordination with the Agency Centers.

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The Investigational Device Exemptions (IDE) regulation (21 CFR 812) describes three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies. In this guidance, we discuss the two types of studies that are subject to the IDE regulation – the SR and NSR studies. For information on studies that are exempt from the IDE regulation, see the Information Sheet Guidance entitled, “Frequently Asked Questions About Medical Devices.”

III. SIGNIFICANT RISK AND NON-SIGNIFICANT RISK DEVICE STUDIES

A. What is a Significant Risk Device Study?

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.

B. What is a Nonsignificant Risk Device Study?

An NSR device study is one that does not meet the definition for an SR device study.

C. Who Decides Whether A Device Study is SR or NSR?

Sponsors are responsible for making the initial risk determination and presenting it to the IRB. FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination.²

Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. If FDA has already made the SR or NSR determination for the study, the agency's determination is final. FDA is available to help the IRB when making its risk determination. (Also, see section VII. “How does an IRB document the SR or NSR determination?”)

² See the guidance entitled, “*Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices.*” This guidance may be found at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126598.

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FDA is the final arbiter as to whether a device study is SR or NSR and makes the determination when an IDE is submitted to FDA or if asked by the sponsor, clinical investigator, or IRB. See 21 CFR § 812.2(b)(1)

D. What are the Major Differences Between SR And NSR Device Studies?

The major differences between SR and NSR studies are in the IDE approval process and in the sponsor's record keeping and reporting requirements, as outlined below.

1. Significant Risk (SR) Device Studies

- SR device studies must follow all the IDE regulations at 21 CFR 812.
- SR device studies must have an IDE application approved by FDA before they may proceed.

2. Nonsignificant Risk (NSR) Device Studies

- NSR device studies must follow the abbreviated requirements at 21 CFR 812.2(b).
- These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. However, there is no need to make progress reports or final reports to FDA.
- NSR device studies do not have to have an IDE application approved by FDA.
- Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. This means that an IRB may approve an NSR device study and an investigator may conduct the study without FDA knowing about it.
- An IRB's NSR determination is important because the IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies. An NSR device study may start at the institution as soon as the IRB reviews and approves the study and without prior approval by FDA.

IV. WHAT ARE THE SPONSOR'S RESPONSIBILITIES WHEN INITIATING A DEVICE STUDY?

A. For Nonsignificant Risk Device Studies

- If the sponsor identifies a study as NSR, the sponsor must provide the reviewing IRB an explanation of its determination (21 CFR 812.2(b)(1)(ii)) and should provide any other information that may help the IRB in evaluating the risk of the study. For example, a

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description of the device, reports of prior investigations with the device, the proposed investigational plan, subject selection criteria, and other information the IRB may need.

- If FDA has determined that the study is NSR, the sponsor should so inform the IRB. By providing such risk determination information to the IRB, the IRB's workload should be reduced and the review process should be facilitated.

B. For Significant Risk Device Studies

- The sponsor must submit an IDE application to FDA and obtain the agency's approval of the study. (See 21 CFR 812.20(a)(1) and (2))
- The sponsor must advise its clinical investigators about the SR status and obtain their agreement to comply with the applicable regulations governing such studies (i.e., 21 CFR Parts, 50, 56, 812) (See 21 CFR 812.43(c)(4)(i)). Sponsors should provide the IDE number and/or a copy of the IDE approval letter to the IRB when requested.
- Sponsors may send their SR device study to an IRB for review before the IDE application is approved by FDA. However, FDA cautions that an SR device study may not begin until FDA approves the IDE.

V. WHAT ARE THE IRB'S RESPONSIBILITIES WHEN IT RECEIVES A DEVICE STUDY FOR REVIEW?

- IRBs should have standard operating procedures that explain how the IRB makes SR and NSR determinations and that the decision should be documented. FDA considers this determination to be part of the IRB's responsibilities for conducting its initial review of a study. (See 21 CFR 56.108)
- IRBs should make the SR or NSR determination about a study by reviewing relevant information at a convened meeting. This information includes the description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria. The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination.
- An IRB may agree or disagree with the sponsor's initial NSR assessment.
- If the IRB determines the study is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to FDA.
- If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must tell the clinical investigator, and where appropriate, the sponsor. (See 21 CFR 812.66)

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- An IRB may approve the study as an SR device study, but the study may not begin until FDA approves the sponsor's IDE application.
- To facilitate the IRB's review of the study, an IRB may ask the sponsor for proof (i.e., a copy of FDA's approval or conditional approval letter) that an SR study has an FDA-approved IDE application.
- The IRB should document its SR/NSR determination in the IRB meeting minutes.

VI. WHAT SHOULD IRBS CONSIDER WHEN MAKING THE SR AND NSR DETERMINATION?

- *What is the basis for the risk determination?* The risk determination is based on the proposed use of a device in an investigation, and not on the device alone.
- *What is the nature of harm that may result from use of the device?* SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject. See the question "What is a Significant Risk Device Study?" for further information.
- *Will the subject need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure?* IRBs should consider the potential harm the procedure could cause as well as the potential harm caused by the device. Several examples follow:
 1. The study of a change to a commercially available pacemaker (e.g., new leads, battery pack, or software) poses an SR because the device is used to support or sustain human life and it presents a potential for serious harm to the subjects. This is true even though the changed pacemaker may potentially pose less risk, or only slightly greater risk, in comparison to the commercially available model.
 2. The study of an extended wear contact lens is SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are NSR.
 3. An investigational study of a sensor pad to find out if the device can detect the electrical activity of the spinal cord may be NSR, if the study of the sensor pad takes place at the same time as the planned surgical repair of the spinal cord, if all the following are true:
 - repair of the spinal cord would occur anyway;

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- the sensor pad does not present a potential for serious risk to the health, safety, or welfare of a subject (for example, placing the pad would not prolong or interfere with the operation);
- the sensor pad is not implanted;
- the pad is not of substantial importance in diagnosing, curing, mitigating or treating disease.

VII. HOW DOES AN IRB DOCUMENT THE SR OR NSR DETERMINATION?

The IRB should write its decision in the meeting minutes. The minutes should describe the IRB's reason for its SR or NSR determination and may also include the documentation used to establish the IDE status for the study. For an SR determination, such documentation may include, for example, a copy of the IDE approval or conditional approval letter from FDA. For an NSR determination, the documentation may include FDA's NSR determination where the agency has made the determination. FDA will issue an NSR letter upon written request.

VIII. WHAT SHOULD AN IRB DO FOR DEVICE STUDIES THAT ARE EXEMPT FROM THE REQUIREMENTS OF THE IDE REGULATIONS (21 CFR 812.2(C))?

For studies that are exempt from the IDE regulations, the IRB does not need to decide whether the study poses a significant risk or nonsignificant risk. However, the IRB must still review the study in accordance with the IRB regulations before the investigation may begin.

IRBs should understand distinctions between certain important concepts that are frequently confused:

A. Difference between NSR and Minimal Risk Determinations

IRBs should not confuse their responsibility to make an SR/NSR determination for a device study with the concept of "minimal risk." "Minimal Risk" is a term used in the IRB regulations in part to identify certain studies that IRBs may approve through an expedited review procedure. For a device study to be eligible for expedited review, it must be an NSR study AND present no more than minimal risk to the subject. (See 21 CFR 56.110)

B. Difference Between SR/NSR Determinations and Approval Decisions

IRBs should not confuse their responsibility to review and approve research for conduct at a clinical site with the SR/NSR determination. IRBs make the SR/NSR determination before the IRB conducts its review of the study under Part 56. The judgment about whether a study poses a significant risk or nonsignificant risk is based on the significance of the potential harm that may result from participation in the study, including the use of the device; whereas

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the IRB's decision to approve a study for implementation is based on the study's risk-benefit assessment.

IX. WHAT ARE FDA'S RESPONSIBILITIES?

- As discussed, FDA is the final arbiter in deciding whether a device study poses a significant or nonsignificant risk. It should be noted, however, that FDA generally only sees those studies that sponsors submit to the agency or those studies for which an IRB or clinical investigator asks for FDA's opinion.
- If FDA disagrees with an IRB's NSR decision and determines that the study poses a significant risk, the sponsor may not begin their study until FDA approves an IDE. (See 21 CFR 812.42)
- If a sponsor submits an IDE to FDA because the sponsor presumed it to be an SR study, and FDA determines that the device study poses a nonsignificant risk, FDA will tell the sponsor in writing. The study may then be reviewed by the IRB as an NSR study.

X. EXAMPLES OF NSR AND SR DEVICES

The following examples may help sponsors and IRBs in making SR and NSR determinations. The list includes many commonly studied medical devices. Inclusion of a device in the NSR list is not a final determination because the evaluation of risk must reflect the proposed use of a device in a study.

A. Nonsignificant Risk Devices

- Caries Removal Solution
- Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use
- Conventional Gastroenterology and Urology Endoscopes and/or Accessories
- Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular)
- Conventional Implantable Vascular Access Devices (Ports)
- Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
- Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)
- Dental Filling Materials, Cushions or Pads made from traditional materials and designs
- Denture Repair Kits and Realigners
- Digital Mammography

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- Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities, measuring depth of anesthesia if anesthetic administration is not based on device output)
- Externally Worn Monitors for Insulin Reactions
- Functional Non-Invasive Electrical Neuromuscular Stimulators
- General Biliary Catheters
- General Urological Catheters (e.g., Foley and diagnostic catheters) for short term use (< 28 days)
- Jaundice Monitors for Infants
- Low Power Lasers for treatment of pain
- Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
- Manual Image Guided Surgery
- Menstrual Pads (Cotton or Rayon, only)
- Menstrual Tampons (Cotton or Rayon, only)
- Nonimplantable Electrical Incontinence Devices
- Nonimplantable Male Reproductive Aids with no components that enter the vagina
- Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
- Partial Ossicular Replacement Prosthesis (PORP)
- Total Ossicular Replacement Prosthesis (TORP)
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain (except for chest pain/angina)
- Ureteral Stents
- Urethral Occlusion Device for less than 14 days
- Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings that aid or are intended to aid in the healing process)

B. Significant Risk Devices

1. General Medical Use

- Catheters for General Hospital Use - except for conventional long-term percutaneous, implanted, subcutaneous and intravascular
- Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications
- Surgical Lasers for use in various medical specialties
- Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

2. Anesthesiology

- Breathing Gas Mixers
- Bronchial Tubes

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- Electroanesthesia Apparatus
- Epidural and Spinal Catheters
- Epidural and Spinal Needles
- Esophageal Obturators
- Gas Machines for anesthesia or analgesia
- High Frequency Ventilators greater than 150 BPM
- Rebreathing Devices
- Respiratory Ventilators and new modes of ventilation
- Tracheal Tubes

3. Cardiovascular

- Annuloplasty Rings
- Aortic and Mitral Valvuloplasty Catheters
- Arterial Embolization Devices
- Atherectomy and Thrombectomy Catheters
- Cardiac Assist Devices: artificial hearts, ventricular assist devices, intra-aortic balloon pumps, cardiomyoplasty devices
- Cardiac Bypass Devices: oxygenators, cardiopulmonary blood pumps, axial flow pumps, closed chest devices (except Class I cardiovascular surgical instruments), heat exchangers, catheters/cannulae, tubing, arterial filters, reservoirs
- Cardiac Mapping and Ablation Catheters
- Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable
- Cardiopulmonary Resuscitation (CPR) Devices
- Cardiovascular Intravascular (vena cava) Filters
- Coronary Artery Retroperfusion Systems
- Distal Embolic Protection Devices
- Extracorporeal Counterpulsation Devices
- Extracorporeal Membrane Oxygenators (ECMO)
- Implantable Cardioverters/Defibrillators
- Intravascular Brachytherapy Devices
- Intravascular Stents
- Laser Angioplasty Catheters
- Organ Storage/Transport Units
- Pacing Leads
- Percutaneous Conduction Tissue Ablation Electrodes
- Percutaneous Transluminal Angioplasty Catheters
- Replacement Heart Valves
- Transcatheter Cardiac Occluders for atrial and ventricular septal defects, patent foramen ovale and patent ductus arteriosus

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- Transmyocardial Revascularization, Percutaneous Myocardial Revascularization Devices
- Ultrasonic Angioplasty Catheters
- Vascular and Arterial Graft Prostheses
- Vascular Hemostasis Devices

4. Dental

- Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
- Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
- Dental Lasers for hard tissue applications
- Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
- Subperiosteal Implants
- Temporomandibular Joint (TMJ) Prostheses

5. Ear, Nose And Throat

- Absorbable Gelatin Sponge
- Auditory Brainstem Implants
- Cochlear Implants
- Endolymphatic Shunt Tubes with or without valve
- ENT Cements/Adhesives
- Implantable Bone Conduction Hearing Aids
- Implantable Middle Ear Hearing Device
- Injectable Teflon Paste
- Laryngeal Implants
- Synthetic Polymer Materials
- Tissue Autofluorescent Devices
- Vocal Cord Medialization (Augmentation) Devices

6. Gastroenterology And Urology

- Anastomosis Devices
- Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
- Biliary Stents
- Components of Water Treatment Systems for Hemodialysis
- Dialysis Delivery Systems
- Electrical Stimulation Devices for sperm collection
- Embolization Devices for general urological use
- Extracorporeal Circulation Systems
- Extracorporeal Hyperthermia Systems
- Extracorporeal Photopheresis Systems

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- Femoral, Jugular and Subclavian Catheters
- Hemodialyzers
- Hemofilters
- Implantable Electrical Urinary Incontinence Systems
- Implantable Penile Protheses
- Injectable Bulking Agents for incontinence
- Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)
- Mechanical/Hydraulic Urinary Incontinence Devices
- Penetrating External Penile Rigidity Devices with components that enter the vagina
- Peritoneal Dialysis Devices
- Peritoneal Shunt
- Plasmapheresis Systems
- Prostatic Hyperthermia or Thermal Ablation Devices
- Retention Type (Foley) Balloon Catheters for long term use (≥ 28 days)
- Suprapubic Urological Catheters and accessories
- Urethral Occlusion Devices for greater than 14 days use
- Urethral Sphincter Protheses
- Urological Catheters with anti-microbial coatings
- Urological Stents (e.g., urethral, prostate, etc.)

7. General And Plastic Surgery

- Absorbable Adhesion Barrier Devices
- Absorbable Hemostatic Agents
- Artificial Skin and Interactive Wound and Burn Dressings
- Breast Implants
- Injectable Collagen
- Implantable Craniofacial Protheses
- Repeat Access Devices for surgical procedures
- Sutures

8. General Hospital

- Implantable Vascular Access Devices (Ports) - if new routes of administration or new design
- Infusion Pumps (implantable and closed-loop - depending on the infused drug)

9. Neurological

- Electroconvulsive Therapy (ECT) Devices
- Hydrocephalus Shunts
- Implanted Intracerebral/Subcortical Stimulators
- Implanted Intracranial Pressure Monitors

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- Implanted Spinal Cord and Nerve Stimulators and Electrodes
- Neurological Catheters (e.g., cerebrovascular, occlusion balloon, etc.)
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of chest pain/angina

10. Obstetrics And Gynecology

- Abdominal Decompression Chamber
- Antepartum Home Monitors for Non-Stress Tests
- Antepartum Home Uterine Activity Monitors
- Catheters for Chorionic Villus Sampling (CVS)
- Catheters Introduced into the Fallopian Tubes
- Cervical Dilation Devices
- Contraceptive Devices:
 - Cervical Caps
 - Condoms (for men) made from new materials (e.g., polyurethane)
 - Contraceptive *In Vitro* Diagnostics (IVDs)
 - Diaphragms
 - Female Condoms
 - Intrauterine Devices (IUDs)
 - New Electrosurgical Instruments for Tubal Coagulation
 - New Devices for Occlusion of the Vas Deferens
 - Sponges
 - Tubal Occlusion Devices (Bands or Clips)
- Cryomyolysis
- Devices to Prevent Post-op Pelvic Adhesions
- Embryoscopes and Devices intended for fetal surgery
- Endometrial Ablation Systems
- Falloposcopes and Falloposcopic Delivery Systems
- Fundal Pressure Belt (for vaginal assisted delivery)
- Gamete and Embryo Surgical Systems
- Intrapartum Fetal Monitors using new physiological markers
- New Devices to Facilitate Assisted Vaginal Delivery
- Operative Hysteroscopy and Laparoscopy
- Uterine Artery Embolization

11. Ophthalmics

- Aniridia Intraocular Lenses (IOLs) or Rings (for iris reconstruction)
- Capsular Tension Rings
- Class III Ophthalmic Lasers

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- Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use
- Corneal Storage Media
- Extended Wear Contact Lens (i.e., including a single overnight use)
- Glaucoma Treatment Devices (e.g., trabeculoplasty devices, devices that treat ciliary bodies, devices that raise or lower intraocular pressure, aqueous shunt/drainage devices, etc.)
- Implants for Refractive Purposes (e.g., intraocular lenses, corneal implants, scleral expansion bands, etc.)
- Intraocular Lenses (IOLs)
- Keratoprotheses
- Refractive Surgical Devices (e.g., lasers, electrical current devices, thermal and non-thermal keratoplasty devices, ablation devices, expansion rings, treatment of ciliary bodies, etc.)
- Retinal Disease Treatment Devices (e.g., electrical stimulation devices to treat macular degeneration, lasers to ablate epiretinal membranes and vitreous strands, etc.)
- Retinal Prosthesis (implant)
- Retinal Reattachment Devices (e.g., fluids, gases, perfluorocarbons, perfluoropropane, silicone oil, sulfur hexafluoride, balloon catheter for retinal reattachment)
- Viscosurgical Fluids (viscoelastics)

12. Orthopedics And Restorative

- Anti-Adhesion Gels
- Bone Growth Stimulators
- Bone Morphogenetic Proteins/Biodegradable Scaffolds combination products, with or without allograft/autograft combinations and with or without metallic implant
- Bone Void Fillers (hydroxyapatite and other materials)
- Bovine Collagen Meniscus Implants
- Computer Guided Robotic Surgery
- Implantable Peripheral Neuromuscular Stimulators
- Implantable Protheses (ligament, tendon, hip, knee, finger)
- Implantable Spinal Devices
- Injectable Sodium Hyaluronate

13. Radiology

- Boron Neutron Capture Therapy
- Hyperthermia Systems and Applicators

Also see the FDA Information Sheet Guidance on “Frequently Asked Questions about Medical Devices.”

Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

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See additional PRA statement in Section 67 of this guidance

For questions regarding this document, contact Sheila Brown, CDRH, at (301) 796-6563 or sheila.brown@fda.hhs.gov or the Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 301-827-1800.



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Program Operations Staff
Center for Biological Evaluation and Research**

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to <http://www.regulations.gov>. When submitting comments, please refer to Docket No. FDA-2008-D-0434. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Center for Devices and Radiological Health (CDRH) through the Internet at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm> You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance document or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (**1668**) to identify the guidance document you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach and Development (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>.

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Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff

Humanitarian Device Exemption (HDE) Regulation: Questions and Answers

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

This guidance document answers commonly asked questions about Humanitarian Use Devices (HUDs) and applications for Humanitarian Device Exemption (HDE) authorized by section 510(m)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). This guidance document reflects the additional requirements set forth in the Pediatric Medical Device Safety and Improvement Act of 2007.

For the purposes of this guidance, “you” refers to the HDE holder, the Institutional Review Board (IRB), or the clinical investigator depending upon how the question is asked and “we” refers to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Definitions

1. What is a Humanitarian Use Device (HUD)?

As defined in 21 CFR 814.3(n), a HUD is a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.”

2. What is a Humanitarian Device Exemption (HDE)?

A Humanitarian Device Exemption (HDE) is an application that is similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of sections 514 and 515 of the Food, Drug, and Cosmetic Act (the Act). FDA approval of an HDE authorizes an applicant to market a Humanitarian Use Device (HUD), subject to certain profit and use restrictions set forth in section 520(m) of the Act. Specifically, as described below, HUDs cannot be sold for profit, except in narrow circumstances, and they can only be used in a facility after an IRB has approved their use in that facility, except in certain emergencies.

3. Who is an HDE holder?

An HDE holder is a person who obtains the approval of a Humanitarian Device Exemption (HDE) from FDA.

4. What does it mean to “use” a HUD?

The term “*use*” in this document, when unmodified, refer to the use of a HUD according to its approved labeling and indication(s) to treat or diagnose patients. When a HUD is being used in a clinical investigation (i.e., collection of safety and effectiveness data), the terms “*investigational use*” or “*clinical investigation*” will be used. A HUD may be studied in a clinical investigation in accordance with its approved indication(s) for a different indication, subject to the requirements described below. For more information on “use” versus “investigational use”/“clinical investigation” of a HUD, see questions 40-42 and “Figure 1: Decision Tree for IRB Review of HUDs” at the end of this guidance.

HUD Designations and HDE Applications

5. What is required in a request for HUD designation?

In accordance with 21 CFR 814.102(a), the applicant’s request must include:

- a statement indicating that the applicant is requesting a HUD designation for a rare disease or condition, or a valid subset of the disease or condition
- the name and address of the applicant

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- a description of the rare disease or condition for which the device is to be used, the proposed indication or indications for use of the device, and the reasons why such therapy is needed
- a description of the device and a discussion of the scientific rationale for the use of the device for the rare disease or condition and
- documentation, with appended authoritative references, to demonstrate that the device meets the definition of 21 CFR 814.3(n).

See 21 CFR 814.102(a) for additional information on each of the above items.

6. When does FDA determine whether a device is eligible for designation as a HUD?

After all supportive materials have been received along with the applicant's request for HUD designation, we determine whether the device is for a rare disease or condition that affects, or is manifested in fewer than 4,000 individuals in the United States (US) per year. In the case of a device used for diagnostic purposes, we also determine at that time whether the documentation demonstrates that fewer than 4,000 individuals per year would be subjected to diagnosis by the device in the United States (21 CFR 814.102(a)(5)).

The applicant should submit the request for a HUD designation before submitting an application for an HDE.

7. Can a device qualify for HUD designation if the affected patient population is fewer than 4,000 per year but there may be multiple contacts with the device for a single patient?

Yes. FDA recognizes that, in some cases, the number of contacts with the device may exceed one per patient. A device that involves multiple patient contacts may still qualify for HUD designation as long as the total number of patients affected, or in which the disease or condition is manifested, is less than 4,000 per year in the US. In the case of a device used for diagnostic purposes, it may also still qualify for HUD designation despite there being multiple contacts with the device by a single patient; the documentation must demonstrate that fewer than 4,000 individuals per year would be subjected to diagnosis by the device in the United States (21 CFR 814.102(a)(5)). That is, devices used in 4,000 or more patients a year to diagnose a subpopulation of less than 4,000 patients with a disease or condition would not be eligible for HUD designation (21 CFR 814.102(b)(3)(ii)).

8. What is required in an HDE application?

The applicant must include a copy of or reference to FDA's HUD designation letter with the HDE application (21 CFR 814.104(b)(1)). Other contents required in an HDE application are described in detail in 21 CFR 814.104. This information enables FDA to

determine whether the device meets the statutory criteria for a HUD set forth in section 520(m)(2) of the Act.

The Pediatric Medical Device Safety and Improvement Act of 2007 (Public Law 110-85) requires additional information in all original HDE applications, if such information is readily available. Specifically, it requires: a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to treat, diagnose, or cure; and the number of affected pediatric patients. See section 515A(a)(2) of the Act.¹

9. Can you submit an HDE application if another comparable device is available to treat or diagnose the disease or condition?

We will consider an HDE application for any of the following:

- no comparable device is available to treat or diagnose the disease or condition; or
- a comparable device is available under another approved HDE application; or
- a comparable device is being studied under an approved Investigational Device Exemption (IDE) (21 CFR 814.104(b)(2)).

However, we cannot approve an HDE for a HUD device once a comparable device with the same indications for use is marketed through either the premarket approval (PMA) process or the premarket notification (510(k)) process. See section 520(m)(2)(B) of the Act.

10. What does FDA consider a “comparable device”?

A “comparable device” need not be identical to the device submitted under the HDE application. In determining whether a comparable device exists, FDA will consider:

- the device's indications for use and technological characteristics
- the patient population to be treated or diagnosed with the device
- whether the device meets the needs of the identified patient population.

Contact Information

11. Where do I submit a request for a HUD designation?

Submit 2 copies of your request for a HUD designation in accordance with 21 CFR 814.102 to:

Office of Orphan Products Development (OOPD)
Food and Drug Administration
WO32-5271

¹ Many of the statutory provisions cited throughout this guidance, including sections 515A(a)(2) and 520(m)(6) of the Act, were added by the Pediatric Medical Device Safety and Improvement Act of 2007.

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10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

If you have questions about the HUD designation, FDA's Office of Orphan Products Development is available at (301) 796-8660.

12. Where do I submit an HDE application?

Submit 6 copies² of your HDE application in accordance with 21 CFR 814.104 to:

For Products Regulated by CDRH

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002.

For Products Regulated by CBER

Document Control Center (HFM-99)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

FDA's Review of HDE Applications

13. How long does FDA have to review an original HDE application?

FDA has 75 days from the date of receipt to approve or deny an HDE application under 21 CFR 814.114. This period includes a 30-day filing period during which we determine whether the HDE application is sufficiently complete to permit substantive review. If we

² We encourage submission of electronic copies. For more information on submission of electronic copies to CDRH, please see "Electronic Copies for Pre-Market Submissions," <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm134508.htm>. For electronic copies submitted to CBER, please see "Regulatory Submissions in Electronic Format for Biologic Products," <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm163685.htm>.

notify the applicant that the application is incomplete and request additional information, the 75-day time frame will reset upon receipt of the additional information by FDA. See section 520(m)(2) of the Act; 21 CFR 814.114.

14. What are the review time frames for HDE amendments, supplements, and reports?

The review timeframe for HDE amendments, supplements, and reports is 75 days, the same as for HDE original applications, except for a supplement submitted as a 30-day notice (21 CFR 814.39(f)).

15. Are HDE amendments, supplements, and reports subject to the same regulations as those for PMAs?

Yes. HDE amendments, supplements, and reports are generally subject to the same regulations as those for PMAs. See 21 CFR 814.106, 814.108, 814.110, and 814.126 for specific HDE requirements.

16. Are HDEs subject to user fees?

No. User fees for HDEs are waived under the Medical Device User Fee and Modernization Act of 2002, as reauthorized and amended by the Medical Device User Fee Amendments of 2007.

17. Does the Quality Systems Regulation (QSR) (21 CFR Part 820) apply to HUDs?

Yes, however, we primarily focus on those manufacturing practices the agency deems most relevant to the safety of the device.

18. Can I request an exemption from the QSR?

Yes. If you believe that you cannot comply with or should not be held to the QSR requirements, you may request an exemption. As described in 21 CFR 820.1(e), the procedures for petitioning for an exemption are set forth in 21 CFR 10.30. In evaluating such a request, we will give overriding consideration to the risks posed by the device, the potential risks that a manufacturing defect might pose, and the public health need for the device.

HDEs and Pediatric Patients

19. If an HDE was approved for use in pediatric patients prior to the enactment of the Pediatric Medical Device Safety and Improvement Act of 2007, is the HDE holder prohibited from profiting from the sale of the device?

Yes, only original HDE applications for devices indicated for use in pediatric patients or in a pediatric subpopulation that are approved on or after September 27, 2007, are assigned an annual distribution number (ADN) and may be sold for profit (subject to restrictions described below). For example, an HDE supplement does not warrant eligibility for profit if the HDE was previously approved before September 27, 2007, for use in pediatric patients or in a pediatric subpopulation.

20. Are separate HDE applications required for a device indicated for pediatric and adult use?

No. Devices that are intended to treat both a pediatric population and an adult population may be included in a single HDE application, but the indications for use should specify use in pediatric patients, or pediatric subpopulation(s), as well as use in adults. In some cases, the safety and probable benefit profile for devices intended for use in a pediatric population, or in a pediatric subpopulation, may differ from its use in an adult population. Therefore, it is recommended that HDE applications for devices intended for use in pediatric populations and adult populations include data supporting the use in both pediatric and adult populations.

We note that the Act, as amended by the Pediatric Medical Device Safety and Improvement Act of 2007 (Public Law 110-85), requires us to establish the annual distribution number (ADN) by assessing projected use of the product in “individuals,” a term that includes both pediatric and adult patients. See section 520(m)(6)(A)(ii) of the Act. This provision authorizes HDE holders to receive profit from the sale of HUDs that are indicated for pediatric use only, or for use in both pediatric and adult patients, subject to the upper limit of the ADN. In this way, when a device is potentially applicable to both pediatric and adult populations, the statute provides an incentive for an applicant to include in its HDE submission to FDA information establishing that the device will not expose pediatric patients to an unreasonable or significant risk of illness or injury and that the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use. Such analysis should address the risks compared to the benefits, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Only when a submission meets this standard for approval will FDA approve the product for use in pediatric patients, and only then will the HDE holder be eligible to receive profit from the sale of the device.

21. What is the annual distribution number (ADN) and how is it determined?

The Pediatric Medical Device Safety and Improvement Act of 2007 (Public Law 110-85) allows HUDs intended for use in pediatric patients or in a pediatric subpopulation and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN is determined by the agency when the agency approves the HDE. It is determined by estimating the number of individuals (pediatric and adult patients) affected by the disease or condition and likely to use the device each year multiplied by the number of devices reasonably necessary to treat each individual. If the number

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calculated is less than 4,000, then this number is the ADN. If the number calculated is equal to or more than 4,000, then the ADN is capped at 3,999 because the ADN must be less than 4,000 devices. See section 520(m)(6)(A)(ii) of the Act.

The applicant should provide supporting data for both the number of individuals likely to use the device each year, and the number of devices reasonably necessary to treat each such individual. The same principles that govern requests for a HUD designation, specifically documentation with appended authoritative references, should apply to requests for an ADN designation. See question 5 for more information on such documentation.

As stated in section 520(m)(8) of the Act, the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is approved.

22. After an HDE is approved and an ADN has been assigned, can an HDE holder request to have the ADN modified?

Yes. An HDE holder may submit an HDE supplement (21 CFR 814.108) requesting modification of the ADN based on new information regarding the number of individuals affected by the disease or condition. Again, the ADN must be less than 4,000.

23. Do HDE holders with ADNs set by the agency have special reporting requirements?

HDE holders assigned an ADN must immediately notify the agency if the number of devices distributed in a year exceeds the ADN. See section 520(m)(6)(A)(iii) of the Act. FDA interprets this statutory requirement to mean that HDE holders must immediately notify the agency by submitting an HDE report whenever the number of devices shipped, or sold, in a year, however they are used, exceeds the ADN.³ In this way, the new statutory notification requirement is generally consistent with the reporting requirement in 21 CFR 814.126(b)(1)(iii) discussed in the "After FDA Approves an HDE" section below (question 31): both concern the number of devices shipped or sold, however the devices are ultimately used (even if outside their approved indications). The only difference is that the new statutory provision requires immediate notification when the number shipped or sold in a year exceeds the ADN, whereas the current regulations require periodic reports on a timeframe specified in the HDE approval order.

³ FDA recognizes that HDE holders may ship additional sizes to facilities to ensure that each device fits properly when used. These additional shipments may or may not count towards the annual ADN tally, depending on whether these additional sizes are used or are returned to the HDE holder.

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In those rare cases in which a device holds both an HDE approval for a certain indication, and a PMA approval for a different indication, sales or shipments of the device pursuant to the PMA are not subject to the ADN reporting requirement. The ADN relates only to those devices that are on the market through the HDE process for a disease or condition that occurs in pediatric patients or in a pediatric subpopulation. In that instance, the manufacturer is only required to notify FDA when sales or shipments tracked pursuant to the HDE exceed the ADN.

24. What happens when the number of devices shipped or sold in a year exceeds the ADN?

For HUDs labeled for use in pediatric patients or in a pediatric subpopulation and approved on or after September 27, 2007, FDA exempts a certain number of these devices each year -- known as the ADN -- from the prohibition on profit (see questions 29 and 30 for more on this prohibition). It is the HDE holder's responsibility to immediately notify the agency in the form of an HDE report (21 CFR 814.126) when the number of HUDs shipped or sold in a year, however they are used, exceeds the ADN. Once this notification occurs, or once FDA discovers through an inspection that the ADN has been exceeded, then the general prohibition on profit applies for the remainder of the year. See section 520(m)(6)(D) of the Act.

25. If a device is manufactured in various sizes depending on a patient's anatomy, the number of devices distributed may be more than the number of devices used in any year. Which number, the number used or the number distributed, is the ADN?

As described above, the ADN is the number of devices shipped or sold in a year that the agency exempts from the prohibition on profit. Once the HDE holder notifies the agency, or once the agency discovers through an inspection, that the ADN has been exceeded, sales of the device for the remainder of the year are subject to the general prohibition on profit. If the HDE holder ships multiple sizes, these shipments may or may not count toward the annual ADN tally, depending on whether these additional sizes are used or are returned to the HDE holder. (See footnote 3.)

26. What is the definition of pediatric patients?

As defined in section 520(m)(6)(E) of the Act, pediatric patients are patients who are 21 years of age or younger at the time of the diagnosis or treatment. A pediatric subpopulation means one of the following populations: neonates, infants, children, or adolescents. FDA reviews pediatric devices through all of its premarket pathways, including premarket notification (510(k)), premarket approval (PMA), biological license application (BLA), and humanitarian device exemption (HDE). Additional information

about the definition of pediatric patients and pediatric use can be found in: “Guidance for Industry and FDA Staff: Premarket Assessment of Pediatric Medical Devices.”⁴

After FDA Approves an HDE

27. Is the HDE holder required to submit to FDA the names and addresses of the IRBs that approved the use of a HUD?

No. The applicant is not required to submit the names and addresses of the reviewing IRBs to FDA. However, as required in 21 CFR 814.126(b)(2), the applicant must maintain records of:

- the names and addresses of the facilities to which the HUD was shipped
- correspondence with reviewing IRBs
- any other information required by a reviewing IRB or FDA.

28. Does the general prohibition on profit apply to HUDs even when used outside their approved indications?

HUDs, even when used outside their approved indications, are subject to the general prohibition on profit. See section 520(m)(3) of the Act; 21 CFR 814.104(b)(5).⁵ As explained in the “HDEs and Pediatric Patients” section above, however, some HUDs are exempt from this prohibition if they are indicated for use in pediatric patients, or in a pediatric subpopulation, or for use in both pediatric and adult patients, subject to the upper limit of the ADN.

For devices that have both an HDE and a PMA approval for a different indication, there is no restriction on profit from sales pursuant to the PMA.

29. How should the HDE holder verify that the amount charged for the device does not exceed the costs of research and development, fabrication, and distribution?

If the HDE holder charges more than \$250 for the device, FDA requires a report by an independent certified public accountant (CPA), or an attestation by a responsible individual of the HDE holder’s organization, verifying that the amount does not exceed the costs of research, development, fabrication, and distribution (21 CFR 814.104(b)(5)). If the amount charged is \$250 or less, this requirement is waived. HDEs for pediatric use approved on or after September 27, 2007, are exempt from the prohibition against

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<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089742.pdf>

⁵ As discussed in a preamble to the HDE Regulation, “an applicant will not be considered in violation of [section 520(m)(3) of the Act] if [the applicant] receives incidental profits which exceed its good faith estimate of costs.” 61 Fed. Reg. 33232, 33242 (June 26, 1996) (citing legislative history).

profiting from the sale of the device up to ADN, as explained in the "HDEs and Pediatric Patients" section above.

30. What adverse event reporting requirements apply to HUDs?

Device user facilities and manufacturers are required to submit medical device reports to FDA and to the "IRB of record" (i.e., the IRB approving the use of the HUD) (See sections 519(a) and (b) of the Act; 21 CFR 803.30, 803.50, and 814.126(a)). Among these requirements, manufacturers must submit reports to FDA and the IRB of record whenever a HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.50 and 814.126(a)). User facilities must submit reports to FDA, the IRB of record, and the manufacturer whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB of record if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a body function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure (21 CFR 803.3). Note: Pediatric adverse events will be reviewed periodically by the agency's Pediatric Advisory Committee (<http://www.fda.gov/oc/advisory/default.htm>). The specific requirements for this reporting are set forth in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803

31. What does the HDE holder need to provide to FDA in its periodic report with respect to the HUD designation?

You must provide us with updated information on a periodic basis demonstrating that the HUD designation is still valid, based on the most current and authoritative information available (21 CFR 814.126(b)). As part of these reporting requirements, you must report the number of devices shipped or sold since initial HDE marketing approval (21 CFR 814.126(b)(1)(iii)). FDA interprets this regulation to require HDE holders to report the total number of devices shipped or sold, no matter how they are used (whether for the approved indication(s), emergency use, or otherwise). However, for devices that have both an HDE approval and a PMA approval for a different indication, you are only required to report on the number of devices that are shipped or sold pursuant to the HDE, unless specifically required by the PMA Approval Order. The required frequency for these periodic reports is specified in each HDE approval order, as explained in 63 Fed. Reg. 59217, 59218 (Nov. 3, 1998).

If, based on information contained in these reports, we believe that the HUD designation may no longer apply to your device, we may contact you for additional information. See 21 CFR 814.126(b)(1) for more information on these reports.

32. Can an HDE holder submit an HDE supplement for a new indication for use of an approved HUD?

No. If you are seeking a new indication for use of an approved HUD, you must first obtain a HUD designation for the new indication for use and then submit a new original HDE application. In the new application, any information or data submitted in the HDE for the original indication may be incorporated by reference. See 21 CFR 814.110.

33. What happens to an approved HDE if, subsequently, FDA makes the determination that the disease or condition affects or is manifested in 4,000 or more individuals in the US per year?

If we make the determination that 4,000 or more individuals in the US are affected or manifest a certain disease or condition per year, we may consider whether the HDE should be withdrawn. We intend to consider factors such as the number of patients with the disease or condition, the feasibility of conducting a pivotal clinical trial (to demonstrate reasonable assurance of safety and effectiveness), and the public health need for the device.

34. If a HUD is being investigated in an IDE study for a different indication, does it impact the number of allowable patients under the HDE?

No. Investigational use of a HUD in an IDE study for a different indication does not impact the HDE approval. The HUD is intended for use in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. The device being investigated in the IDE study for possible subsequent PMA approval or 510(k) clearance will not be for the same indications for use as the HUD.

35. After FDA approves an HDE for a HUD, if FDA subsequently approves a PMA or clears a 510(k) for the device or another comparable device with the same indication, what is the status of the HDE approval?

If we subsequently approve a PMA or clear a 510(k) for the HUD or another comparable device with the same indication, we may withdraw the HDE. Once a comparable device becomes legally marketed through PMA approval or 510(k) clearance to treat or diagnose the disease or condition in question, there may no longer be a need for the HUD and so the HUD may no longer meet the requirements of section 520(m)(2)(B) of the Act.

The Role of Institutional Review Boards (IRBs)

36. What are the differences between an HDE and an IDE? They both use “device exemption” in their titles and can thus be confusing to IRBs.

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Quite simply, the term “exemption” for the HDE means that certain statutes and regulations need not be followed in order to legally market a HUD. An HDE approval is based on safety and probable benefit; HDEs are exempt from the requirement to provide a reasonable assurance of effectiveness, as otherwise required in sections 514 and 515 of the Act.

The term “exemption” for the IDE means certain statutes and regulations need not be followed in order to study an unapproved or uncleared device (or an approved or cleared device for an unapproved or uncleared indication) in a research study involving humans (i.e., an IDE is an investigational exemption). With this exemption, the unapproved or uncleared device can be shipped and used in human research.

We remind IRBs that question 4 of this document makes a distinction between “use” of a HUD and “**investigational use**”/ “**clinical investigation**” of a HUD. The term “use” in this document, when unmodified, refers to the use of a HUD according to its approved labeling and indication(s). If a HUD is being used in a clinical investigation (i.e., collection of safety and effectiveness data), whether for its HDE-approved indication(s) or for a different indication, then this document refers to “investigational use” or “clinical investigation” of the HUD. Such investigational use is subject to the same requirements that apply to all FDA-regulated clinical studies, including 21 CFR Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards). Additionally, if the HUD is being studied for a use other than its approved indication(s), the IDE regulations at 21 CFR Part 812 apply. See questions 40-42.

For a schematic view of the difference between “use” and “investigational use”/“clinical investigation” of a HUD, please refer to “Figure 1: Decision Tree for IRB Review of HUDs” at the end of this guidance.

37. Should an IRB be concerned if there is a HUD approved for one indication, while the same device is being studied or marketed for another indication that does not qualify for an HDE?

No. As stated above, a HUD may be used in accordance with its approved indication(s) for use while the same device is being studied under an IDE for a different indication. Additionally, the same device can be approved or cleared for another indication without impacting the HDE.

38. What are the differences between a PMA, 510(k) and an HDE?

Three regulatory paths to the market for devices are via Premarket Approval (PMA), Premarket Notification (510(k)), and HDE.

A device with an approved PMA is approved for marketing based on valid scientific evidence and reasonable assurance that the device is safe and effective for its intended use. Once approved, it can be marketed and sold within its approved labeling. There are no restrictions on the price, and it can be used by anyone qualified to use the device.

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A 510(k) device is cleared for marketing when the agency finds that it is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not required to have a PMA. Using valid scientific evidence, submitters compare their device to one or more similar legally marketed devices, comparing the indications for use and technological characteristics. Once cleared, it can be marketed and sold in accordance with its labeling. There are no restrictions on the price, and it can be used by anyone qualified to use the device.

A device with an approved HDE is approved for marketing, but the approval is based on evidence of safety and probable benefit. The Act and implementing regulations exempt HUDs from the requirement to establish a reasonable assurance of effectiveness. The HUD is intended for use in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the US per year. The manufacturer of a HUD can make a profit, subject to the limit of the ADN, only if it is indicated for use in a pediatric population or subpopulation or for use in both pediatric and adult patients, was approved on or after September 27, 2007, and with certain other restrictions. (See the “HDEs and Pediatric Patients” section above for further discussion of this profit allowance.) Another important difference is that HUDs require IRB approval before being used at a facility. See sections 520(m)(3), (4), (6) of the Act; 21 CFR 814.124.

39. How does an IRB distinguish between the use of a HUD and the study of a HUD in a clinical investigation (i.e., research)?

Prior to the approval of an HDE application for a device, any studies conducted using the device must be under the IDE regulations (21 CFR Part 812). Once the HDE is approved, the following information applies if a clinical investigator or the HDE holder wants to conduct a clinical investigation using the HUD.

An HDE holder may collect safety and effectiveness data in a clinical investigation **for the HDE-approved indication(s)** without an IDE. As long as the HUD is being studied in accordance with the approved indication(s) described in labeling, the HUD, as such, is legally marketed and can be lawfully shipped without an IDE. See 21 CFR 812.1. IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50) are still required for these studies because they are FDA-regulated clinical studies.

Clinical investigation of a HUD **for a different indication** must be conducted in compliance with the IDE regulations at 21 CFR Part 812, in addition to requiring IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50). If the device is a significant risk device, an FDA-approved IDE is required. See 21 CFR 812.1, 812.20. To date, all HUDs have been significant risk devices requiring FDA-approved IDEs. See question 42 for more discussion of significant risk devices.

In short, IRB approval, informed consent, and additional safeguards for children (if applicable) are required for the **clinical investigation (investigational use) of a HUD,**

whether the HUD is being studied for its HDE-approved indication(s) or for a different indication. These requirements are separate and distinct from the requirements that apply to the **use of a HUD** at a facility: as described in questions 43 and 59, IRB approval is required before a HUD is used at a facility to treat or diagnose patients and the IRB may require informed consent as part of such approval. In other words, just because an IRB has approved use of a HUD at a facility to treat or diagnose patients does **not** mean that the IRB has approved investigational use of the HUD (i.e., in a clinical investigation), for the collection of safety and effectiveness data. For more information on the difference between "use" of a HUD and "investigational use"/"clinical investigation" of a HUD, see "Figure 1: Decision Tree for IRB Review of HUDs" at the end of this guidance.

40. What if the HDE holder decides to collect safety and effectiveness data in a study to support a PMA for the HDE-approved indications?

As stated above, you may collect safety and effectiveness data to support a PMA for the HDE-approved indication(s) without an IDE. While the work done to collect such safety and effectiveness data to support a PMA constitutes a clinical investigation, FDA considers the study exempt from the requirement for an IDE as long as the HUD is used in accordance with its approved indication(s). IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50) are still needed, however, as required for all FDA-regulated clinical studies. As noted above, the IRB approval, informed consent, and additional safeguards for children (if applicable) required for the clinical investigation/investigational use of a HUD are separate and distinct from the IRB approval and any consent associated with the use of the HUD. That an IRB has approved use of a HUD at a facility to treat or diagnose patients does **not** mean the IRB has approved investigational use of the HUD (i.e., in a clinical investigation), for the collection of safety and effectiveness data.

If you want to collect safety and effectiveness data for a use other than the HDE-approved indication(s), you must comply with the IDE regulations at 21 CFR Part 812 in addition to complying with the requirements for IRB approval (21 CFR Part 56) and protection of human subjects (21 CFR Part 50).

41. Does an IRB have to make the determination of a significant risk (SR) or non-significant risk (NSR) device (21 CFR 812.66) when it reviews a HUD?

When an IRB is deciding whether to approve use of a HUD at a facility (see questions 43-52), its review does not include an SR/NSR determination. As noted above, use of a HUD at a facility to treat or diagnose patients is not a "clinical investigation"; the HUD as such is legally marketed for use within its HDE-approved indication(s).

If an IRB receives a request to review a clinical investigation of a HUD (i.e., collection of safety and effectiveness data), and that clinical investigation concerns the **HDE-approved indication(s)**, then again the IRB does not have to make an SR/NSR determination in its review. FDA considers such investigations exempt from the IDE

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requirements in 21 CFR Part 812, as noted above. Nonetheless, the IRB still has to approve the clinical investigation under 21 CFR Part 56 and informed consent and additional safeguards for children (if applicable) are required under 21 CFR Part 50, as for all FDA-regulated clinical studies.

In contrast, if the IRB receives a request to review an application for an investigational study of the HDE for a **different indication**, then the IRB should be alert that this type of clinical investigation is subject to the IDE regulations at 21 CFR Part 812. To date, all HUDs when studied for uses other than their approved indication(s) have been SR devices requiring an FDA-approved IDE. See 21 CFR 812.20(a). In practice, most sponsors have obtained an IDE from FDA before beginning such studies, and so IRBs have not needed to make the SR/NSR determination (i.e., the sponsors already knew their device was an SR device). However, in the event that a sponsor seeks IRB approval for research of a HUD for an indication other than its approved indication(s) without first obtaining an FDA-approved IDE, then the IRB should make the SR/NSR determination as described in 21 CFR 812.66.

42. Is IRB approval required before the use of a HUD at a facility?

Yes. As stated in section 520(m)(4) of the Act, IRB approval is required before a HUD is used at a facility, with the exception of emergency use (see question 65). The IRB must have among its members (or consultants) the appropriate experience and expertise to perform a complete and adequate review of the use of a HUD at that institution (21 CFR 56.107(a)). In addition, a local IRB may defer in writing to another similarly constituted IRB that has agreed to assume responsibility for review of the use of the HUD. This deferral letter must be sent to the HDE holder, because the HDE holder is responsible for ensuring that a HUD is administered only in facilities in which the reviewing IRB is constituted and acting in accordance with 21 CFR Part 56 (21 CFR 814.124(a)). See question 46 for further discussion of the scope of IRB approval.

43. Who is responsible for submitting materials to and obtaining approval from the IRB before the HUD is used at a facility?

As explained above, the HDE holder is responsible for ensuring that the HUD is administered only in facilities with properly constituted and functioning IRBs (see question 27). The health care provider at such facilities should be responsible for obtaining IRB approval before use of the HUD, except in certain emergencies where prior IRB approval is not required (see question 65). The IRB should have policies and procedures in place for receipt and evaluation of the materials necessary for initial approval and continuing review of the HUD.

44. How should an IRB evaluate requests for approval of the use of a HUD?

As stated in 21 CFR 814.124(a), an IRB that reviews and approves the use of a HUD must be constituted and act in accordance with the agency's regulation governing IRBs (21 CFR Part 56), which include initial and continuing review of the use of the device. FDA recommends that an IRB follow the review criteria at 21 CFR 56.111 and elsewhere

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in Part 56 as much as possible. For example, you should review the risks to patients that are found in the product labeling, ensure the risks are minimized, and evaluate whether the risks are reasonable in relation to the proposed use of the device.

Specifically, FDA recommends reviewing the following materials during initial review of the HUD: a copy of the HDE approval order; a description of the device; the product labeling; the patient information packet that may accompany the HUD; a sample consent form for the use of the HUD, if required by the IRB; and a summary of how the physician proposes to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures. A list of approved HDEs may be found at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2>.

The approval order, labeling, and patient information may be found by selecting the number of the appropriate HDE. You should have policies and procedures in place for this review and approval, including whether your IRB requires a consent document for the use of the HUD.

45. To what extent should an IRB exercise oversight of clinician responsibilities in the use of a HUD?

In reviewing the use of the HUD, IRBs should be cognizant that the FDA has made a determination of safety and probable benefit for use of the HUD only within its approved indication(s). The IRB is not required to review and approve each individual use of a HUD. Rather, the IRB may use its discretion to determine how to approve use of a HUD. For example, if it so wishes, with the input of members with the appropriate expertise in the clinical area (21 CFR Part 56), an IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB or IRB chairperson, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate.

46. What types of review functions are IRBs responsible for with respect to HUDs?

IRBs are responsible for initial as well as continuing review of the HUD. For initial review of a HUD, IRBs are required to perform their review at a convened meeting (21 CFR 56.108). For continuing review, IRBs may use the expedited review procedures (21 CFR 56.110). When applicable, review of the use of a HUD and review of the investigational use of a HUD in a clinical investigation may be done simultaneously.

47. Why does FDA suggest that an IRB perform the continuing review of a HUD using an expedited procedure?

FDA recommends the use of an expedited procedure because a HUD is a legally marketed device and no safety and effectiveness information is being collected systematically, as is required for a research protocol. An expedited review does not mean a less than substantive review. During the expedited review, the Chair or the Chair's

designated member(s) should thoughtfully consider the risk and benefit information available and any Medical Device Reporting (MDR) reports (see question 50). IRBs may develop their own policies and procedures for continuing review of a HUD and may perform this review at a convened meeting.

48. Should other committees at an institution be involved in the review of a HUD?

There is no regulatory requirement for committees other than the IRB to approve the use of a HUD. However, the institution may require additional review. For example, the use of another committee to provide assessments of specific risk posed by the technology or software compatibility may supplement the IRB review.

49. What does an IRB have to know about Medical Device Reporting (MDR)?

The HDE regulation, 21 CFR 814.126(a), requires that MDR reports submitted to FDA, in accordance with 21 CFR Part 803 (see question 31) shall also be submitted to the "IRB of record" (i.e., the IRB approving the use of the HUD).

50. What should an IRB consider with respect to the health care provider(s) who will use the HUD?

The IRB may want to ensure that health care providers are qualified through training and expertise to use the device. For many HDEs, the HDE holder is required to provide training on the use of the device prior to the health care provider using the device. Such requirements would be specified in the HDE approval order, available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2> (select the HDE number).

51. Must an IRB request a protocol to review before approving the use of the HUD?

When a HUD is used to treat or diagnose patients, i.e., not for research, we do not require submission of a protocol to the IRB for review. However, your IRB or institution may require one under its own policies and procedures.

52. Does FDA require an IRB to monitor the number of uses per year of a HUD?

No. It is the responsibility of the HDE holder to monitor how many devices are distributed each year, and if that number exceeds 4,000, to provide an explanation and estimate of how the device is being used by patients. See 21 CFR 814.126(b)(1)(iii).

53. Must an IRB review or audit the medical record of patients who received a HUD?

No, we do not require you to audit medical records of patients who receive a HUD.

54. Should an IRB ask for justification of the charges for the HUD?

No. There is no requirement for the IRB to request a justification of the charges for the HUD. FDA reviews the financial information in the HDE holder's initial application, and periodically thereafter.

55. Should an IRB be concerned if an HDE holder charges for a HUD?

HDE holders generally charge for the HUD that is used to treat or diagnose a patient. However, HUDs cannot be sold for a price that exceeds the costs of research and development, fabrication, and distribution of the device. The exception is if they are indicated for use in a pediatric population, or pediatric subpopulation, or for use in both pediatric and adult patients, were approved on or after September 27, 2007, and annual sales have not yet exceeded the ADN (as discussed in "HDEs and Pediatric Patients" section above). See sections 520(m)(4), (6) of the Act.

If a HUD is studied in a clinical investigation of a new indication, the sponsor of the clinical investigation may not charge subjects or investigators a price larger than necessary to recover the costs of manufacture, research, development, and handling (21 CFR 812.7(b)). Any costs for which a subject in a clinical investigation is responsible must when appropriate, be clearly explained in the informed consent document (21 CFR 50.25(b)(3)).

56. Does an IRB function as a Data Monitoring Committee for a HUD?

No. The IRB may, however, ask the HDE holder for copies of the safety information submitted to FDA in the periodic reports required by 21 CFR 814.126(b)(1). In this way, information that could have a bearing on human safety would be considered at the time of continuing review.

57. Do the requirements for review of a HUD change if an IRB has a Federal Wide Assurance (FWA) with the Department of Health and Human Services, Office for Human Research Protections?

No. The use of a HUD is not research; rather, it is use of a legally marketed device. We describe the IRBs responsibilities in section 520(m) of the Act and in the implementing regulations at 21 CFR 814.124. We also offer guidance to you in this document. If, however, a HUD is used in a clinical investigation (see question 41), IRBs should follow their FWA requirements and their written procedures for FDA-regulated research.

58. What information should be given to patients before they receive a HUD, and should patients consent to the HUD use?

Neither the Act nor the regulations require informed consent from patients for the use of a HUD. An IRB may, however, choose to require informed consent that is consistent with the approved labeling when the IRB approves use of the HUD in a facility.

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Most HDE holders develop patient information packets that generally contain a discussion of the potential risks and benefits of the HUD and any procedures associated with its use. If patient information packets are available, the IRB should ensure that physicians distribute them to patients prior to their receiving the HUD. Even when an institution requires patients to sign a written consent document that describes the use of the HUD (and which may provide similar information found in the HDE holder's packet), the patient should always receive the HDE holder's patient information packet. For HUD patient information packets, go to

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2> and select the HDE number. In addition to the above information, many institutions also require informed consent for the surgery or procedure related to the use of the HUD. If a HUD is studied in a clinical investigation, the informed consent of the subject must be obtained in accordance with FDA regulations at 21 CFR Part 50 (see question 41).

59. If an IRB requires a written consent document for the use of a HUD, what information should be included?

It would be reasonable for the document to include much of the information found in the HDE holder's patient information packet. If no patient information packet is available, you may consider including the following: an explanation that the HUD is designed to diagnose or treat the disease or condition described in the HDE labeling and that no comparable device is available to treat the disease or condition; a description of any ancillary procedures associated with the use of the HUD; a description of the use of the HUD; all known risks or discomforts; and an explanation of the postulated mechanism of action of the HUD in relation to the disease or condition. You should also include information reflecting the HUD status of the device, such as a sentence indicating that the effectiveness of this device for this use has not been demonstrated. The IRB may decide to include other information.

If the HUD is studied in a clinical investigation, the elements included in the informed consent document must conform to the requirements found in 21 CFR 50.25.

60. Is it appropriate for the HUD labeling and materials to include the phrase "FDA approved"? What other information must the labeling contain?

HUD labeling and materials must be truthful and not misleading. See section 502(a) of the Act. The labeling may state that the device is approved as a HUD for its intended use, but the labeling must also include the following statement clarifying that effectiveness has not been demonstrated: "Humanitarian Device. Authorized by Federal law for use in the [treatment or diagnosis] of [specify disease or condition]. The effectiveness of this device for this use has not been demonstrated." See 21 CFR 814.104(b)(4)(ii) for more information on HUD labeling requirements.

61. What should IRBs tell physicians who want to study a HUD for a new indication?

Physicians who want to study a HUD for a new indication must submit an IDE application to FDA if the device is a significant risk device (see question 42). Physicians may be either the sponsor or investigator of the study or they may want to involve the HDE holder as the sponsor. The investigational use of a HUD under these circumstances is a clinical investigation and must be conducted in accordance with 21 CFR Parts 812, 50, 54, and 56.

62. Does the use of a HUD constitute treatment or research under the Health Insurance Portability and Accountability Act of 1996 (HIPAA)? Does the IRB need to waive a HIPAA authorization for the use or disclosure of protected health information related to the use of a HUD?

The Privacy Rule promulgated at 45 CFR Parts 160 and 164, Subparts A and E pursuant to HIPAA governs the use and disclosure of certain individually identifiable health information (protected health information). An entity that is covered by HIPAA (a covered entity) may use and disclose protected health information without the patient's authorization if the use or disclosure is for the purpose of treatment. If the use or disclosure of protected health information is for the purpose of research, then the covered entity generally must obtain the patient's authorization, unless an IRB or Privacy Board has determined that such an authorization is not necessary because the research satisfies certain waiver criteria.

The use of a HUD according to its approved labeling and indication is generally for treatment or diagnosis, even though such use requires IRB approval. If a HUD is being used according to its approved labeling and indication, and not in a clinical investigation, then protected health information about a patient may be used or disclosed for treatment or diagnostic purposes without the patient's authorization under HIPAA.

If a HUD is being used in a clinical investigation, whether or not the use of the HUD is the subject of the investigation, then protected health information about a patient that is used or disclosed for purposes of the clinical investigation requires the patient's authorization under the HIPAA Privacy Rule. The IRB may waive this authorization if certain waiver criteria are met.

63. Does reporting of safety and effectiveness data to the sponsor require a HIPAA authorization or does this activity fall under an FDA-related activity under 45 CFR 164.512(b) (public health reporting)?

Reporting HUD safety information to the sponsor does not require a HIPAA authorization since it falls under the permissive disclosure for FDA-related activities at 45 CFR 164.512(b)(iii).

Using HUDs in Emergency Use Situations

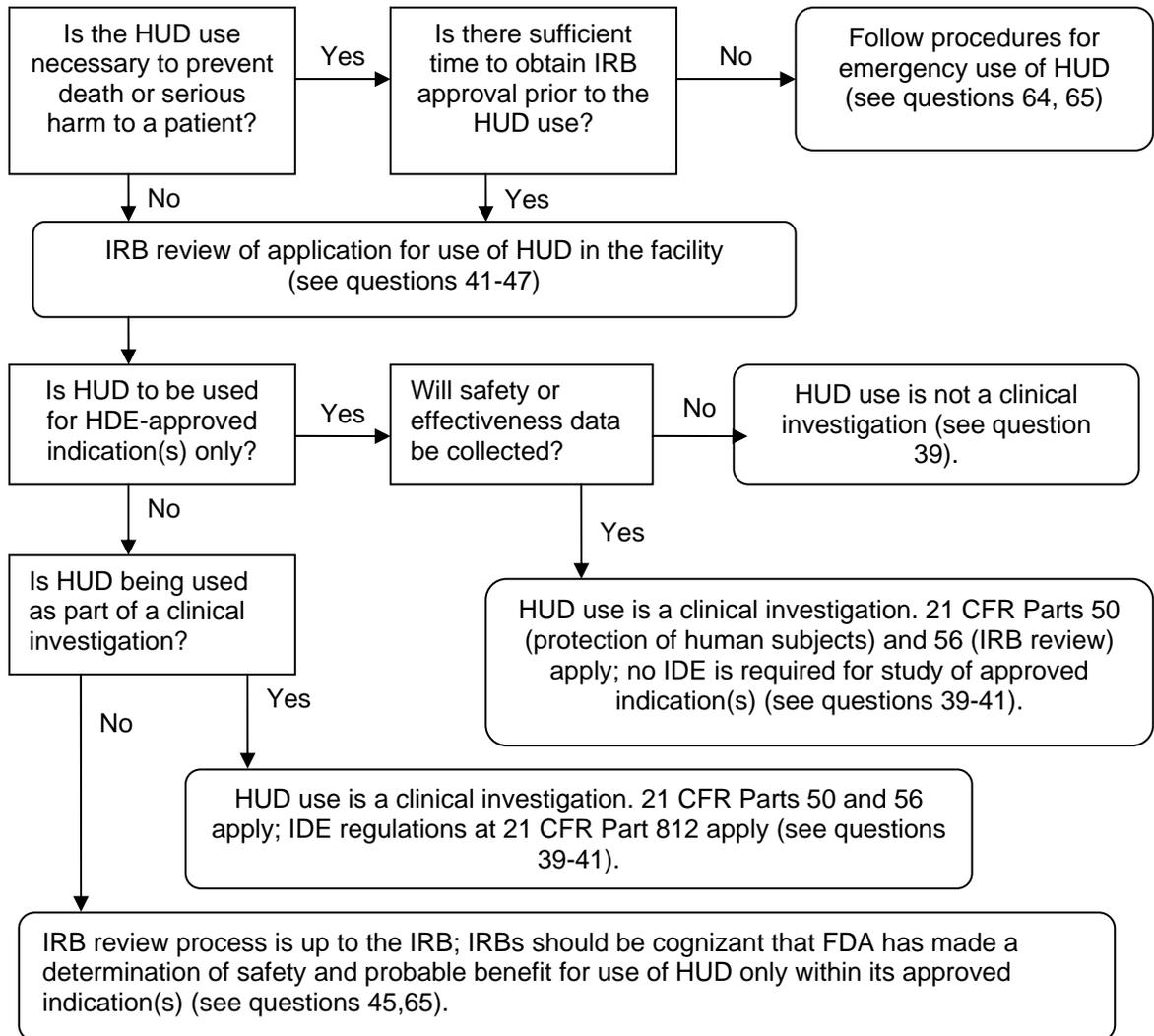
64. When can a HUD be used without prior IRB approval?

If a physician in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The physician must report the emergency use within five days; provide written notification of the use to the IRB chair person including identification of the patient involved, the date of the use, and the reason for the use. See section 520(m)(4) of the Act; 21 CFR 814.124.

65. After an IRB approves the use of the HUD at the facility, can a physician use a HUD outside its approved indication(s) in an emergency or if the physician determines there is no alternative device for the patient's condition?

Physicians should be cognizant that FDA has made a determination of safety and probable benefit for use of the HUD only within its approved indication(s). If a physician wants to use a HUD outside its approved indication(s), FDA recommends that the physician obtain informed consent from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient, taking into consideration the patient's specific needs and the limited information available about the risks and benefits of the device. FDA further recommends that the physician submit a follow-up report on the patient's condition to the HDE holder and first check with the IRB before such use to review any institutional policy. The extent of IRB oversight in these circumstances is up to the IRB (see questions 45 and 46). Note: as discussed in question 30, MDR reports must be submitted to FDA and to the "IRB of record" (i.e., the IRB approving the use of the HUD) if the device may have caused or contributed to death or serious injury and for certain malfunctions.

Figure 1: Decision Tree for IRB Review of HUDs



Note: Medical device reporting is required under 21 CFR Part 803 whenever the use of a HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (see questions 30, 49, 65). For investigational use of a HUD under an IDE, reports of unanticipated adverse device effects must be reported under 21 CFR 812.150(a)(1) and 812.150(b)(1).

Section 508 text for Figure 1.

66. Flowchart. Is the HUD use necessary to prevent death or serious harm to a patient? If no, proceed to node 1; if yes, is there sufficient time to obtain IRB approval prior to the HUD use? If yes, proceed to node 1; if no, Follow procedures for emergency use of HUD (see questions 64, 65). Node 1, IRB review of application for use of HUD in the facility (see questions 41-47). Is HUD to be used for HDE-approved indication(s) only? If no, proceed to node 2; if yes, will safety or effectiveness data be collected? If yes, HUD use is a clinical investigation. 21 CFR Parts 50 (protection of human subjects) and 56 (IRB review) apply; no IDE is required for study of approved indication(s) (see questions 39-41). If no, HUD use is not a clinical investigation (see question 39). Node 2, is HUD being used as part of a clinical investigation? If yes, HUD use is a clinical investigation. 21 CFR Parts 50 and 56 apply; IDE regulations at 21 CFR Part 812 apply (see questions 39-41). If no, IRB review process is up to the IRB; IRBs should be cognizant that FDA has made a determination of safety and probable benefit for use of HUD only within its approved indication(s) (see questions 45, 65).

67. Paperwork Reduction Act of 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The time required to complete this information collection is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
HDE Program WO66-1645
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR part 803 have been approved under OMB control number 0910-0437; the collections of information in 21 CFR part 812 have been approved under OMB control number 0910-0078; the collections of information in 21 CFR part 807, subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 814, subparts A, B, and C have been approved under OMB control number 0910-0231; the collections of information in 21 CFR parts 50 and 56 have been approved under OMB control number 0910-0130; the collections of information in 21 CFR part 820 have been approved under OMB control number 0910-0073; the collections of information in 21 CFR part 814, subpart H have been approved under OMB control number 0910-0332; and the collections of information in 21 CFR 10.30 have been approved under OMB control number 0910-0183.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

The OMB control number for this information collection is 0910-0661, which expires on 05/31/2013.

INVESTIGATIONAL NEW DRUGS

A drug is defined as (15 U.S.C. 55(c)):

- An article recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them.
- An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.
- An article (other than food) intended to affect the structure or any function of the body of man or other animals.
- An article intended for use as a component of any article specified in clause (A), (B), or (C).

- I. A drug is considered *investigational* when it is used as part of a clinical investigation. A clinical investigation is any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

II. Investigational Drugs Subject to IND Regulations

The FDA may make an IND or IND Exempt determination. The IRB may make an IND Exempt determination. If the IRB thinks a device may be subject to the IND regulations, then the investigator must submit it to the FDA for further review. An IND is required for all clinical investigations that involve a drug, unless the clinical investigation is found to be otherwise exempt from the requirement for an IND. The sponsor/investigator should make the initial determination if the investigation is exempt. If the HRPO/IRB agrees, the investigation may proceed. If the HRPO/IRB disagrees, the investigator must submit an application to the FDA. The FDA will make the final determination as to whether an IND is required. The investigation may not proceed until this has been finalized.

- **Sponsor or Sponsor-Investigator IND (21 CFR 312.3).**
 - i. If a sponsor or investigator intends to conduct a clinical investigation with an investigational new drug, the investigation may not begin until the IND has been approved by the FDA.
 - ii. An IND is required for all clinical investigations that are not exempt. The requirements for exemption are listed below.
- **Treatment IND (21 CFR 312.300).**
 - i. If an investigational drug has shown promise in clinical testing for serious or immediately life threatening conditions for which there is no alternative therapy, access to the investigational drug may be permitted through an FDA approved treatment IND.
 - ii. A Treatment IND is typically granted for “expanded access use” only if an investigational drug is in FDA final risk evaluation stages. Data collected during the study will support potential FDA approval, but the consent form should not describe the study as research as it involves a treatment protocol.

III. Investigational Drugs Not Subject to IND Regulations

- *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 (21 CFR 312.2(b)):*
 - 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 concerning the promotion and sale of drugs (21 CFR 312.7 – Promotion of investigational drugs.)

INVESTIGATIONAL NEW DRUGS – STUDIES INVOLVING A WASHOUT PERIOD

An investigator may intend to test the safety and efficacy of an investigational drug, which may require participants to discontinue the use of drugs they are currently taking in order to eliminate variables that may confound or distort data collected during the study.

- I. In this case, the investigator will need to provide a management plan that contains the following:
 - A protocol for withdrawing participants in the event that their disease or condition worsens due to their participation in a placebo arm or phase of the study.
 - A description of the method and frequency of contact with participants in the placebo arm or phase of the study.
 - A list of contacts available on a 24/7 basis for questions or emergencies during the placebo phase of a study.

- II. In order to evaluate the proposed plan, the IRB will need to discuss the following:
 - *Is the washout a necessary element of the study design?*
 - *Are the risks related to the proposed washout period outweighed by the potential benefits of the research?*
 - *Does the management plan sufficiently minimize any risk related to the washout period?*

Guidance for Industry

IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**January 2004
Clinical Medical**

Revision 1

Guidance for Industry

IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer

Additional copies are available from:

*Office of Training and Communications
Division of Drug Information, HFD-240
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573*

(Internet) <http://www.fda.gov/cder/guidance/index.htm>

or

*Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448*

(Internet) <http://www.fda.gov/cber/guidelines.htm>.

Mail: the Voice Information System at 800-835-4709 or 301-827-1800

**U.S. Department of Health and Human Services
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Revision 1

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**Guidance for Industry¹
IND Exemptions for Studies of Lawfully Marketed
Drug or Biological Products for the
Treatment of Cancer**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if that approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors in deciding whether a study of marketed drugs or biological products for treating cancer falls within the exemption under § 312.2(b)(1) (21 CFR 312.2(b)(1)) from the general requirement to submit an investigational new drug application (IND). The guidance discusses the Agency's current thinking on when studies of marketed cancer products are exempt from IND regulation based on a risk assessment. The Agency hopes that clarifying its policy will help sponsors identify which studies are exempt, thus saving them from submitting unnecessary IND applications.

This guidance revises the guidance of the same title published in September 2003. In the September 2003 version, the Agency's final statement was that it believed that most randomized studies of a size that could support a labeling supplement would likely *not* be exempt from IND regulation under § 312.2(b)(1)(i), (ii). This is because they would be intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising. Experience has shown that this interpretation was formulated too broadly and inappropriately referred to size alone. The Agency has decided to revise this guidance by removing that statement (the last sentence in section V.B). Whether a study could support a change in labeling is a complex determination, based on study design, size, and other factors.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Division of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER) and by the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Generally, regulations in part 312 (21 CFR part 312) require sponsors who wish to study a drug or biological product in humans to submit an IND to the Agency.² However, these regulations also provide for the exemption of some studies from the requirement to submit an IND if they meet certain criteria. Each year, many INDs for cancer drugs are submitted that contain studies that the Agency determines are exempt. This guidance is intended to help applicants identify which studies may be exempt.

A. Regulations

Regulations in § 312.2(b)(1) provide for the exemption of some studies for some drugs from IND regulations if the studies meet the following five criteria:

1. The study is not intended to support FDA approval of a new indication or a significant change in the product labeling.
2. The study is not intended to support a significant change in the advertising for the product.
3. 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.
4. The study is conducted in compliance with institutional review board (IRB) and informed consent regulations set forth in parts 56 and 50 (21 CFR parts 56 and 50).
5. The study is conducted in compliance with § 312.7 (promotion and charging for investigational drugs).

Requirements 1, 2, 4, and 5 are not directly related to the specific protocol submitted, and their interpretation is similar for oncologic and nononcologic therapies. Requirement 3 is protocol related and has special meaning in the oncology therapy setting, particularly with respect to doses above the labeled dose, use with other treatments, and use in different populations.

In the preamble to the IND regulations, which published in the *Federal Register* on March 19, 1987, the Agency explained that the exemption was not necessarily intended to tie the investigator to the doses and routes of administration and patient population described in the

² Part 312 applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

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approved labeling, but to permit deviations from the approved labeling to the extent that such changes are supported by the scientific literature and generally known clinical experience. The Agency recognizes that a considerable amount of professional judgment is exercised in determining whether the planned investigation significantly increases the risk associated with the use of the drug. FDA maintains that “because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption.”³

B. 1996 Agency Cancer Initiative

In 1996, as part of the President's National Performance Review, the Agency launched its *Reinventing the Regulation of Cancer Drugs* initiative with the goal of accelerating the approval of and expanding patient access to cancer drugs.⁴ As part of this initiative, the Agency explained that many sponsor-investigators were submitting INDs for exploratory studies for so-called off-label indications for two reasons: (1) IRBs incorrectly believe an IND is required, or (2) the pharmaceutical manufacturer agrees to provide a drug free of charge, but mistakenly concludes that the FDA will view this as promotional activity. With the intent of clarifying the Agency's policy and decreasing the number of unnecessary submissions, the Agency emphasized that it would no longer accept INDs considered exempt under § 312.2(b)(1). (See § 312.2(b)(4).) Furthermore, FDA stated that providing a drug for study would not, in and of itself, be viewed as a promotional activity if the manufacturer or distributor provides the product for a physician-initiated, bona fide clinical investigation. The Agency explained that it is the responsibility of the investigator to determine whether an IND is necessary.

Despite the Agency's attempts to clarify its policy on IND exemptions, many cancer drug IND applications that the Agency determines are exempt from IND regulation are still being submitted unnecessarily. From 1997 to 1999, a majority of investigator IND submissions for marketed cancer drugs were considered exempt (204, 205, and 140 applications in 1997, 1998, and 1999, respectively).

III. RISK/BENEFIT ANALYSIS IN THE PRACTICE OF ONCOLOGY

As noted above, a critical question in determining whether a study is exempt involves criterion 3 in the exemption regulations (§ 312.2(b)(1)(iii)): The investigation may not *significantly increase the risk* associated with use of a drug product. The question of increased risk is determined by assessing the deviation in the planned investigation from the use described in the approved label. In oncology, modifications of labeled dosing recommendations are common and

³ New Drug, Antibiotic, and Biologic Drug Product Regulations, *Federal Register*, March 19, 1987, Vol. 52, Nr. 53, p. 8802.

⁴ *Reinventing the Regulation of Cancer Drugs – Accelerating Approval and Expanding Access* (March 1996), CBER, Office of Communication, Training, and Manufacturer Assistance, Voice Information System at 1-800-835-4709 or 301-827-1800, document ID number 0281. Available on the Internet at <http://www.fda.gov/cber/genadmin/reincanc.htm>

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occur as part of oncologists' clinical practice. As outlined below, oncologists are familiar with evaluating the risk of off-label dosing regimens for cancer drug and biological products.

- Treatment with cancer drugs may be associated with significant risk from known toxicity. Because effectiveness is often related to dose, a dose close to the *maximal tolerated dose* is often selected for studies of cancer drugs. This same dose usually becomes the recommended dose in labeling when the new cancer drug is approved with the knowledge that the dose may be altered if it is not tolerated by a patient. Because it is not generally possible to have maximal efficacy in a population without inducing toxicity in some patients, it is not uncommon to observe severe or even lethal side effects from cancer drugs in some patients. In general, these circumstances mean that the toxicity, even potentially lethal toxicity, of cancer drugs is described in approved labeling.
- Off-label therapy with cancer drugs is common in practice. When there is no established therapy for a cancer, or stage of cancer, it is common for oncologists to try different regimens or combinations of established drugs. A 1996 GAO report (*Prescription Drugs, Implications of Drug Labeling and Off-Label Use*) showed that there was substantial off-label use in situations where satisfactory treatment was not available, and lower rates of off-label use when there was an effective therapy. In their daily practice, many oncologists treat cancer patients with regimens that include off-label use of drugs. They evaluate the published data and past clinical experience to assess the risk of such treatments. Such treatment of individual patients with approved drugs within their clinical practice does not require an IND (§ 312.2(d)).
- In many cases, as discussed in the examples in section V below, drug administration to patients with similar off-label regimens in the context of an investigation seems to involve no increased risk to patients, and an investigator could conclude that such a study would not *significantly increase the risk* associated with the labeled use of a drug product and the study could be conducted without an IND. Oversight by an IRB and informed consent in compliance with parts 56 and 50, respectively, would be required as usual (§ 312.2(b)(1)(iv)). On request, FDA will advise on the applicability of the IND exemption to a planned clinical investigation (§ 312.2(e)).

IV. DETERMINING APPLICATION STATUS

A. Agency Determination

As explained in FDA's 1996 cancer initiative and the IND exemption regulation, FDA will not accept applications for clinical studies that it determines to be exempt from the requirement for an IND (§ 312.2(b)(4)). Although § 312.2(b)(1) does not require a submission for a determination of exempt status, whenever an IND application is submitted, FDA staff perform an initial limited review of the application to determine whether the study is exempt. The protocol-related criterion FDA considers in assessing exemption is: The investigation may 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

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use of the drug product (§ 312.2(b)(1)(iii)). Thus, when determining if the risk is significantly increased, FDA staff examine the parts of the protocol that concern dose, schedule, route of administration, and patient population. If the Agency's initial limited review determines that a study protocol is exempt from the requirement for an IND, the Agency performs no further review of the application. A letter is sent to the sponsor giving notice of the exemption.

B. Investigator Determination

When determining if an IND needs to be submitted to study marketed drugs for treating cancer, investigators must apply the exemption criteria listed in § 312.2(b)(1)(i-v) in light of the discussion in this guidance. Planned studies may be considered exempt from the requirements of an IND if the studies involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a patient population with cancer and the following conditions apply:

- The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
- The studies are not intended to support a significant change in the advertising for the product.
- Investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no *significant increase in the risk associated with the use of the drug product*.
- The studies are to be conducted in compliance with IRB and informed consent regulations, pursuant to parts 50 and 56.
- The studies will not be used to promote unapproved indications, in compliance with § 312.7.

V. EXAMPLES OF STUDIES

The following examples of studies are being provided to illustrate the Agency's current thinking on the types of studies that the Agency considers to be exempt from IND regulation based on a risk assessment.

A. Studies That Generally Are Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely be exempt from IND regulation based on protocol-related issues.

1. Single-arm, phase 2 trials using marketed drugs to treat a cancer different from that indicated in the approved labeling and using doses and schedules similar to those in

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the marketed drug labeling are usually exempt. An exception may exist when standard therapy in the population to be studied is very effective (e.g., is associated with a survival benefit); in that case, use of another regimen may expose patients to the risk of receiving an ineffective therapy and an IND would be necessary.

2. Phase 1 oncology trials of marketed drugs may be considered exempt if such therapy is appropriate for the patient population (i.e., if patients have residual cancer) and if there is no effective therapy (i.e., therapy producing cure or a documented increase in survival) that the patients have not yet received. It remains the investigator's responsibility to use starting doses that appear safe based on approved labeling or detailed literature reports, use incremental changes in dose or schedule, and carefully evaluate toxicity prior to dose escalation.
3. The study of new combinations of drugs would not ordinarily constitute a significant risk if these combinations have been described in the professional medical literature. Even when the regimen described in the literature does not use exactly the doses planned for study, incremental differences in doses from those described in the literature would not normally pose a significant risk and would not require an IND.

Because of the danger of synergistic toxicity (i.e., enhanced effects from the combination) occurring with a new drug combination, if there are no data from the literature on its safety, the initial study of a new drug combination should ordinarily be performed under an IND. Synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent. If it is determined that synergistic toxicity is likely, animal studies should be considered for determining a safe starting dose for the drug combination in humans.

4. Studies of new routes or schedules of administration not described in the approved labeling are generally exempt if there is sufficient clinical experience described in the literature documenting safety to determine that treatment is safe. On the other hand, initial experience with a new route of administration should be based on studies in animals, and an IND should be submitted.
5. Studies of high-dose therapy in cancer patients are likely to be considered exempt if the studies use adequately evaluated regimens that appear to have an acceptable therapeutic ratio for the population being studied. Similarly, phase 1 studies involving incremental changes from such well-described regimens are generally exempt.

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B. Studies That Generally Are Not Exempt

As noted above, of the five criteria in § 312.2(b)(1), four are not protocol related and one is protocol related. The following are examples of general categories of studies of marketed cancer drugs that would likely *not* be exempt from IND regulation because of protocol-related issues.

1. Studies of cytotoxic drugs are normally not exempt in patients for whom cytotoxic therapy would not be considered standard therapy and would require special justification. Any use of cytotoxic agents in nonmalignant disease (e.g., rheumatoid arthritis, multiple sclerosis) would, most likely, be considered to alter the acceptability of the risk of the agent.
2. Studies of adjuvant chemotherapy (chemotherapy given after surgery to remove cancer) are likely not exempt for the following reasons:
 - If the population studied has a low risk of cancer recurring after surgery, treatment with any toxic therapy may indicate a significantly increased risk.
 - If standard adjuvant therapy is available and produces a survival benefit, substitution of new therapy for standard therapy poses a significant risk that the new therapy will not produce the same survival benefit.
 - If adjuvant trials are properly designed, they usually will be able to demonstrate whether the new therapy is safe and effective, and such results may lead to a marketing application. As discussed earlier, under regulations at § 312.2(b)(1), all investigations intended to support marketing of a new product indication, significant change in product labeling, or a significant change in the advertising for a product require an IND. During FDA review of INDs intended to support marketing applications, the Agency will provide feedback about the acceptability of trial design for this purpose.
3. Studies involving substitution of a new agent of unproven activity are generally not exempt in settings where standard therapy provides a cure or increase in survival. For instance, in the first-line treatment of testicular cancer, ovarian cancer, breast cancer, leukemia, and lymphoma, studies of new agents without proven efficacy would likely not be exempt. In this case, the critical judgment is whether it is ethical to withhold standard therapy while testing a new agent.
4. Studies are generally not exempt in settings where animal studies should be conducted to determine a safe starting dose or schedule.

For example:

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- Initial studies of a marketed drug given by a new route of administration are likely not exempt.
 - Unless adequately described in the literature, initial studies of new drug combinations should usually be performed under an IND because of the possible occurrence of synergistic toxicity. As noted earlier, synergistic toxicity may be anticipated when one agent interferes with the metabolism or elimination of the other agent; when both agents target the same metabolic pathway or cellular function; or when one agent targets signaling pathways that are reasonably expected to modulate sensitivity to the other agent.
 - Initial studies in humans of changes in the schedule of drug administration should generally be submitted in an IND. Some drugs have demonstrated significantly greater toxicity when given by an alternative schedule (e.g., methotrexate demonstrates much more hematologic toxicity when given by prolonged administration compared to intermittent administration).
 - Initial studies of drugs intended to be chemosensitizers, radiosensitizers, or resistance modulators should generally be submitted in an IND. Animal studies should be used to estimate the effect of the modulator on toxicity and to allow estimation of a safe starting dose in humans.
5. Studies intended to support approval of a new indication, a significant change in the product labeling, or a significant change in advertising are not exempt (§ 312.2(b)(1)(i), (ii)).

MOTIONS – IRB MEETING

- I. The following motions can be made during an IRB meeting to initiate a vote regarding the approvability of a study. The IRB can propose different motions for different research components or populations. The chair will initiate one of the following motions:
- **A Motion to Approve**
 - i. *Made when a study meets all of the criteria for approvability (45 CFR 46.111, 21 CFR 56.111) without any additional revisions.* (HRPO Staff can be asked to correct specified typographical errors in the application or study documents, or add non-substantive language to the consent as specified by the IRB.)
 - ii. Requires a statement regarding the length of approvability for the study. A study can be approved for a maximum of one year from the date of the meeting.
 - iii. Requires a statement regarding the regulatory category of approval for the enrollment of pregnant women and neonates, prisoners, and/or children where applicable. Also note any applicable waivers.
 - iv. Requires an indication of risk level, either minimal risk or more than minimal risk.

 - **A Motion to Approve Pending**
 - i. *Made when a study meets all of the criteria for approvability (45 CFR 46.111, 21 CFR 56.111), but the IRB has noted specific revisions to the application or study documents.* The response of the investigator to these requested revisions can be reviewed by HRPO staff for mere concurrence with the IRB findings. If the revisions reference elements that require scientific expertise to review, the IRB can designate a member to review the response of the investigator (such as the primary or secondary reviewer).
 - ii. Requires a statement regarding the length of approvability for the study. A study can be approved for a maximum of 365 days from the date of the meeting.
 - iii. Requires a statement regarding the regulatory category of approval for the enrollment of pregnant women and neonates, prisoners, and/or children where applicable. Also note any applicable waivers.
 - iv. Requires an indication of risk level, either minimal risk or more than minimal risk.

 - **A Motion to Table**
 - i. *Made when a study does not meet all of the criteria for approvability (45 CFR 46.111, 21 CFR 56.111), but may be approvable if significant revisions are made to the application or study documents, or the IRB is provided with information not currently present in the application.*
 - ii. The response of the investigator will be reviewed by HRPO staff for concurrence with the findings of the IRB. These revisions will be scheduled for review at the nearest available meeting of the committee that voted to table the study.

 - **A Motion to Disapprove**
 - i. *Made when a study does not meet all of the criteria for approvability (45 CFR 46.111, 21 CFR 56.111) due to a fundamental ethical concern regarding study design, study outcomes, a study population, or any element of the proposed research.* The investigator has the right to directly appeal to the committee that disapproved a study at the nearest available meeting of that committee.

II. Examples of Motions:

A new study, modification, or CR that has no contingencies:

"I move to approve the study as greater than minimal risk with no contingencies. It can be approved for one year."

A study with contingencies involving children and significant risk, but the prospect of benefit:

"I move to approve the study as greater than minimal risk with the contingencies we have discussed. The response can be reviewed by HRPO staff. Because it is a Phase II trial involving children, it should be reviewed again in 6 months. Because the study holds the prospect of direct benefit to children, it meets the 46.405 category. The signature of only one parent is required."

A study with contingencies that require scientific expertise to review:

"I move to approve the study as greater than minimal risk with the contingencies we have discussed. There is sufficient information to determine the criteria for approval have been met, however these contingencies involve information regarding radiology that should be reviewed by the Primary Reviewer. It can be approved for one year."

A study with a waiver of consent:

"I move to approve the study as minimal risk. It can be approved for one year. The criteria for a Waiver of Consent are met: it is minimal risk because it only involves, the rights of participants are protected by....., the research could not be conducted without the waiver because....., and there is no need to contact participants with information about the study"

A study that is tabled :

"I move to table the study. We do not have sufficient information to determine whether the consent and assent process is appropriate as the investigator needs to provide a plan for the assent of the children they intend to enroll. This plan will need to come back to the IRB for review before it can be approved."

VOTING – IRB MEETING

If an IRB member has a conflict of interest with a study (such as a financial interest or membership on the study team) currently being reviewed, that IRB member may not participate in voting, and must remain outside the board room while this voting is being conducted. The IRB member may be available for questions during the discussion of the study.

- I. When a motion is proposed and seconded, the IRB will vote regarding the proposed motion.
- II. IRB members may make the following responses:
 - Vote to *Agree*
 - Vote to *Abstain*
 - Vote to *Disagree*
- III. A majority of votes in agreement is required for the motion to be approved.
- IV. A record of the number of votes for each response will be recorded anonymously in the IRB meeting minutes. In the event that a member is recused due to a conflict of interest, the person with the conflict and reason for recusal is documented in the minutes. If a member is absent during the voting regarding a study for any other reason, this absence will be recorded by name, but no reason will be documented.

Guidance on IRB Approval of Research with Conditions

This guidance represents OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word *must* in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word *should* in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches by telephone at 240-453-6900 or 866-447-4777, or by email at ohrp@hhs.gov.

Date: November 10, 2010

Scope: This document applies to non-exempt human subjects research conducted or supported by HHS. It provides guidance on the authority of institutional review boards (IRBs) to approve research with conditions. In particular, OHRP offers guidance on the following topics:

A. What actions can an IRB take when reviewing research?

B. What does *IRB approval with conditions* mean?

C. What circumstances preclude the IRB from approving research?

D. What circumstances permit the IRB to approve research with conditions?

E. How should the IRB handle changes to research that are proposed after the IRB has approved the research with conditions?

F. How do conditions on IRB approval at the time of initial review affect the initiation of research?

G. May an IRB approve some components of a proposed research study and defer taking action on other components at the time of initial review?

H. How do conditions on IRB approval at the time of continuing review, or at the time of review of proposed changes in previously approved research, affect ongoing research?

I. What must the IRB records include regarding the documentation of conditions of IRB approval of research?

Target Audience: IRBs, investigators, HHS funding agencies, and others that may be responsible for the review, conduct, or oversight of human subjects research conducted or supported by HHS.

Regulatory Background:

An IRB must review proposed research, including proposed changes to previously approved research, at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except when expedited review is authorized (45 CFR 46.108(b) and 46.103(b)(4)). In order for research to be approved, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)).

IRBs reviewing research have the authority to approve, require modifications in (to secure approval), or disapprove the research (45 CFR 46.109(a)).

An IRB may use the expedited review procedure to review either or both of the following:

- (1) Some or all of the research appearing on the list of categories of research that may be reviewed by the IRB through an expedited review procedure (see <http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm>);
- (2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. (45 CFR 46.110).

HHS regulations at 45 CFR 46.102(h) define *IRB approval* as the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

In order to approve research, IRBs must determine that all of the following requirements are satisfied in accordance with HHS regulations at 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 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 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.
- (8) 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

When applicable, IRBs must determine that the additional protections of subpart B (Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research), subpart C (Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects), or subpart D (Additional Protections for Children Involved as Subjects in Research) of 45 CFR part 46 have been met.

Guidance:

A. What actions can an IRB take when reviewing research?

Given the authorities that IRBs have under HHS regulations at 45 CFR 46.109(a), when conducting an initial or continuing review of a research study, or a review of proposed changes to a previously approved research study, an IRB can take any of the following actions:

- (1) Approve the research study or proposed changes either (a) as submitted without any conditions, or (b) with conditions (note that, as explained in section B below, when

- research is approved by the IRB with conditions at a convened meeting, further review by IRB at a subsequent convened meeting is not necessary);
- (2) Require modifications to secure approval and defer or table the research study or proposed changes for further review at a future date after the required modifications are submitted by the investigator; or
 - (3) Disapprove the research study or proposed changes.

B. What does *IRB approval with conditions* mean?

In the course of initial or continuing review of research, or review of proposed changes to previously approved research, IRBs often request that investigators (a) make specified changes to the research protocols or informed consent documents; or (b) submit clarifications or additional documents. When doing this, depending on the circumstances, the IRB is either:

- (1) precluded from approving the research, as described in section C below; or
- (2) permitted to approve the research with conditions, as described in section D below.

By *IRB approval with conditions* (sometimes referred to as “conditional approval” or “contingent approval”), OHRP means that at the time when the IRB reviews and approves a research study (or proposed changes to a previously approved research study), the IRB requires as a condition of approval that the investigator (a) make specified changes to the research protocol or informed consent document(s), (b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or (c) submit additional documents, such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46. With respect to research reviewed and approved with conditions by the IRB at a convened meeting, note that because the IRB is able to make all these determinations, the IRB may designate the IRB chairperson (and/or other individual(s) with appropriate expertise or qualifications) to review responsive materials from the investigator and determine that the conditions have been satisfied, and further review by the IRB at a subsequent convened meeting would not be necessary.

C. What circumstances preclude the IRB from approving research?

Any time the IRB reviewing a research project cannot make one or more of the determinations required for approval by the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46, the IRB must not approve the research project. This applies to both initial and continuing review of research, and review of proposed changes to previously approved research.

For example, the IRB must not approve a proposed research project undergoing initial review when the IRB (a) is unable to make the required determinations about research risks and benefits, the adequacy of privacy and confidentiality protections, or the adequacy of the informed consent

process because the research protocol provides insufficient information related to these aspects of the research, and (b) is unable to specify changes to the research protocol that if made would allow the IRB to make these required determinations.

When an IRB reviewing a research project at a convened meeting is unable to approve research because it cannot make the determinations required for approval, the IRB can either disapprove the project, or defer or table the project for further review at a future date. When deferring or tabling the project, the IRB, under its authority to require modifications in order for an investigator to secure approval, may require that the investigator (a) make changes to the protocol or informed consent documents, or (b) submit clarifications or additional documents prior to the next review. If the IRB defers or tables a research project, the research may not proceed until the IRB reviews the revised research project and approves it at a subsequent convened meeting.

When an IRB reviewing a research project under an expedited review procedure is unable to approve the project because the chairperson (or designated reviewer(s)) cannot make the determinations required for approval, the IRB chairperson (or designated reviewer(s)) can either refer the project to the IRB for further review and action at a convened meeting, or defer approval of the research project and require that the investigator (a) make changes to the protocol or informed consent documents, or (b) submit clarifications or additional documents prior to further review by the IRB chairperson (or designated reviewer(s)). Research may not be disapproved under an expedited review procedure (45 CFR 46.110(a)).

Examples of required changes or clarifications that generally would preclude the IRB from approving the research include the following:

- (1) Providing a justification for using a placebo and withholding currently available treatment for a serious medical condition for subjects assigned to a control group (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1) and (2));
- (2) Providing a justification for enrolling children in the research and an explanation of how the research would satisfy the requirements of subpart D of 45 CFR part 46 (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under subpart D of 45 CFR part 46);
- (3) Revising the study hypothesis and, accordingly, the study design (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1), (2), and (4));
- (4) Providing a description of procedures that the control group will undergo (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1), (2), and (4));
- (5) Providing clarifying information needed to assess the risks to subjects, such as clarifying whether individuals who have taken aspirin within 14 days prior to enrollment will be

excluded from the study because of concerns about the risks of bleeding (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1) and (2); see example (5) in section D below for an alternative approach that would allow the IRB to approve the research with conditions);

- (6) Clarifying the timing and circumstances under which the informed consent of prospective subjects will be sought (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(4); see example (6) in section D below for an alternative approach that would allow the IRB to approve the research with conditions); or
- (7) providing a plan to implement additional subject monitoring in order to reduce risks to subjects, given the number of serious adverse events that have occurred in study subjects since the prior IRB review (OHRP notes that in this example the IRB would need the investigator's response in order to make the determinations under 45 CFR 46.111(a)(1), (2), and (4)).

D. What circumstances permit the IRB to approve research with conditions?

The IRB may approve research with conditions if, given the scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C, or D of 45 CFR part 46. The authority to approve research with conditions extends to the IRB's initial review of research, continuing review of research, and review of proposed changes to previously approved research. This authority also applies to IRB review of research at a convened meeting or under an expedited review procedure.

The IRB may require the following as conditions of approval of research:

- (1) Confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (e.g., confirmation that the research excludes children);
- (2) Submission of additional documentation (e.g., certificate of ethics training);
- (3) Precise language changes to protocol or informed consent documents; or
- (4) Substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, verification procedures must be included as part of the IRB approval process, under which the IRB chairperson (and/or other individual(s) designated by the IRB) will review responsive materials from the investigator required by the IRB, and determine whether the conditions of approval have been satisfied (45 CFR 46.102(h)). The IRB's verification that the investigator has satisfied all conditions of approval stipulated by

the IRB helps to ensure that the investigator does not initiate any research that is different from what was approved by the IRB (45 CFR 46.102(h)).

Note that OHRP does not consider this verification process by the IRB chairperson or any other individual designated by the IRB to represent the review and approval of minor changes under an expedited review procedure. As a result, IRBs have significant flexibility regarding who may be designated to verify that conditions have been satisfied, including designation of someone other than an IRB member.

Individuals designated by the IRB to review responsive materials from the investigator and determine whether the IRB's conditions for approval have been satisfied should have appropriate expertise or qualifications. Depending upon the nature of the required conditions, the IRB could designate any of the following individuals or groups of individuals to determine that the conditions of approval have been satisfied:

- The IRB chairperson;
- Another IRB member or group of IRB members with particular subject matter expertise or experience;
- A consultant with particular subject matter expertise who is not an IRB member; and/or
- An IRB administrator or other qualified IRB administrative staff person, who need not be an IRB member.

For some conditions, the review of responsive materials from investigators will require medical, scientific, or other technical expertise. In such cases, the IRB should designate an individual having the appropriate expertise to review the responsive materials from the investigator; typically, this would be the IRB chairperson, another IRB member, or an expert consultant. For others conditions for which the investigator simply needs to make verbatim changes to the protocol or informed consent document or to submit a specific document, review of the responsive materials from investigators typically will not require any special expertise. In these cases, the IRB could designate an IRB administrator or other IRB administrative staff person to review the responsive materials from the investigator.

The following examples illustrate the types of conditions IRBs could stipulate when approving research, as well as the type of individual who might be designated by the IRB to determine that the conditions of approval have been satisfied; these examples are not intended to be all-inclusive, nor are they intended to suggest that the type of individual designated in the example is either appropriate or necessary in all such circumstances:

- (1) Requiring submission of documentation of an endorsement letter from a department chair, as required by institutional policy, and designating an IRB administrator or other qualified IRB staff member to confirm receipt of the required documentation;
- (2) Requiring correction of minor grammatical and typographical errors in the informed consent document, and designating an IRB administrator or other qualified IRB staff member to review the revised informed consent document and confirm that the required corrections were made;

- (3) Requiring that a listed investigator provide a copy of his approved clinical privileges/hospital staff appointment document in order to confirm that he has approval to perform the procedures (e.g., percutaneous liver biopsies) proposed in the research protocol at the institution where the research is to be conducted, and designating an IRB administrator or other qualified IRB staff member to review this document and confirm that the clinical privileges of the listed investigator include authorization to perform such procedures.
- (4) Requiring that the investigator re-locate in the informed consent document the statement “You will receive \$500 for participating in this study” from the “Benefits” section of the form to a separate section under the heading “Compensation,” and designating an IRB administrator or other qualified IRB staff member to review the revised informed consent document and verify the re-location;
- (5) Requiring that the investigator – in order to ensure that risks to subjects are minimized – add “a history of aspirin use in the past 14 days” to the exclusion criteria for subject enrollment in the research protocol, and designating an IRB administrator or other qualified IRB staff member to review the revised protocol and verify that the stipulated language was added to the exclusion criteria;
- (6) For a randomized clinical trial comparing two types of surgical procedures, requiring that the investigator – in order to ensure that informed consent will be obtained under circumstances that provide prospective subjects with sufficient opportunity to consider whether or not to participate – revise the protocol to indicate that informed consent of the prospective subjects will be sought by the investigator during an outpatient clinic visit at least one week before the surgery, and designating an IRB administrator or other qualified IRB staff member to review the revised protocol and verify that the requested language regarding the process for soliciting informed consent of the prospective subjects was added to the protocol.
- (7) Requiring the investigator to (a) confirm that any standard contrast material used in radiological procedures dictated by the research protocol will be limited to agents and dose levels specified in precise detail by the IRB, and (b) submit a revised protocol which includes the precise agents and dose levels, and designating an IRB administrator or other qualified IRB staff member to review the revised protocol and verify that the changes made by the investigator match those specified by the IRB;
- (8) Requiring that the investigator modify the informed consent document to include standard template language used for research involving college psychology students, stating that comparable non-research alternatives for earning extra credit will be offered to students who choose not to participate in the research, and designating an IRB administrator or other qualified IRB staff member to review the revised informed consent document and verify the addition;

- (9) Requiring the addition to the informed consent document of a description of the risks of a standard chemotherapy drug, where the risks are well-described in the research protocol, and designating an IRB member or consultant who is knowledgeable about those risks to review the revised informed consent document and confirm that the description of the risks is satisfactory;
- (10) Requiring revision of the research protocol to include a description of the type and amount of standard contrast material to be used in the radiological procedures dictated by the research protocol, and designating an IRB member or consultant who is a radiologist to review the revised protocol and ensure that the use of standard contrast material is medically appropriate;
- (11) Requiring simplification of the description of the study risks in the informed consent document to be at an 8th grade comprehension level, and designating the IRB chairperson to review the revised informed consent document and ensure that risks are accurately described and understandable at an 8th grade comprehension level;
- (12) Requiring that the research protocol be revised to include a plan for (a) informing subjects about the results of standard clinical tests performed as part of the research protocol (e.g., cardiac function tests), and (b) referring subjects for appropriate clinical follow-up, and designating an IRB member or a consultant with appropriate clinical expertise (e.g., a cardiologist) to review the revised protocol and confirm that the plan is medically appropriate.

E. How should the IRB handle changes to research that are proposed after the IRB has approved the research with conditions?

After research has been approved with conditions by the IRB, additional changes are sometimes proposed by the investigator or recommended by designated reviewers before all conditions have been satisfied and the protocol documents have been finalized. The process for handling such changes is the same as for any change that is proposed during the period for which IRB approval has already been given (see 45 CFR 46.103(b)(4)(iii)).

Protocol corrections that are only administrative in nature (e.g., correction of typographical and spelling errors in the protocol) would not need additional IRB review because OHRP does not consider such corrections to be changes to the research.

Changes to the research that are “minor” may be reviewed by the IRB chairperson or by another experienced reviewer designated by the chairperson from among the members of the IRB under an expedited review procedure in accordance with 45 CFR 46.110(b)(2). OHRP notes that under 45 CFR 46.110(c), all members of the IRB must be advised of any such minor changes that are approved under an expedited review procedure.

Changes to the research that are more than minor would require further review by the IRB at a convened meeting.

OHRP recommends that institutions adopt policies for determining the types of changes in previously approved research that constitute “minor” changes which can be approved under an expedited review procedure, in contrast to greater than minor changes which require review by the IRB at a convened meeting.

F. How do conditions on IRB approval at the time of initial review affect the initiation of the research?

Whenever the IRB approves a research study with one or more conditions at the time of initial review, the effective date of the initial approval is the date on which the IRB chairperson (or any other individual(s) designated by the IRB) has reviewed and accepted as satisfactory any revised protocol or informed consent documents or any other responsive materials required by the IRB from the investigator. (For additional guidance on determining the effective dates of IRB approval and continuing review dates, see OHRP’s *Guidance on IRB Continuing Review of Research* at <http://www.hhs.gov/ohrp/policy/continuingreview2010.pdf>.) In these circumstances, no research study activities involving human subjects may be initiated until the conditions have been satisfied in the manner set forth by the IRB and the approval becomes effective.

Once the investigator has responded to the IRB’s conditions, if the designated reviewer(s) determines that the responsive materials do not satisfy the conditions of approval stipulated by the IRB, then the IRB approval has not become effective, and the investigator may not proceed with the research. The investigator may submit additional revisions or material to the IRB for review by the designated reviewer(s) in an attempt to satisfy the IRB’s conditions, or may choose to submit a modified research proposal to the IRB. If the investigator chooses not to submit any additional revisions or materials to the IRB for review by the designated reviewer(s), then the approval for the research activity would not become effective, and the investigator may not conduct the research study.

When someone other than the IRB chairperson is the designated reviewer and the designated reviewer and investigator are unable to agree on whether the responsive material provided to the IRB by the investigator satisfies the conditions of approval, OHRP recommends that the designated reviewer and investigator consult with the IRB chairperson or that the matter be referred to the convened IRB.

G. May an IRB approve some components of a proposed research study and defer taking action on other components at the time of initial review?

Yes, at the time of initial review an IRB may approve some components of a proposed research study and allow an investigator to initiate research activities only related to those approved components, while deferring taking action on other components of the proposed study. In such circumstances, the IRB must ensure that the approved components of the research study are scientifically valid and satisfy all criteria required for IRB approval, even if the other components are never approved and conducted. The IRB may require that the investigator, in order for the investigator to secure approval for the unapproved components of the initially proposed research study, submit to the IRB for review (a) changes to the protocol or informed

consent documents, or (b) clarifications or additional documents. The following example further illustrates this scenario:

- (1) The investigator proposes a research study involving the enrollment of subjects ages 12-65 years, including pregnant women.
- (2) Because the investigator did not provide sufficient information regarding the involvement of children and pregnant women, the IRB is unable to make the findings required for approval under subparts B and D of 45 CFR part 46. As a result, the IRB approves the research study for one year only for involvement of non-pregnant adult subjects, and the research may not involve pregnant women or children. Note that the IRB must ensure that the study as initially approved without inclusion of children or pregnant women is scientifically valid and satisfies all criteria for IRB approval under 45 CFR 46.111.
- (3) The IRB requires that the investigator, in order to secure approval for inclusion of pregnant women and children in the study, submit additional information necessary for the IRB to make the findings required under subparts B and subpart D of 45 CFR part 46.
- (4) The investigator subsequently submits sufficient information necessary for the IRB to make the determinations required under subparts B and D. The IRB reviews this information, makes the required determinations, and approves the involvement of children and pregnant women in the study. At this point, the investigator can begin enrolling pregnant women and children.

H. How do conditions on IRB approval at the time of continuing review, or at the time of review of proposed changes in previously approved research, affect ongoing research?

When approving research with conditions at the time of continuing review, or at the time of review of proposed changes to previously approved research, the IRB should be careful to specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions. For example, if at the time of continuing review the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure.

Likewise, if at the time of continuing review, or at the time of review of proposed changes to previously approved research, the IRB requires that the investigator within 30 days (a) change the informed consent document to include a description of a newly identified risk, and (b) submit a written plan for informing currently enrolled subjects about the new risk, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised informed consent document and verifies that the description of the new risk has been added. Alternatively, the IRB could stipulate that no further research activities involving human subjects (including activities of already enrolled subjects) may occur after the

date of the IRB's continuing review or the review of the protocol changes until the investigator has submitted, and the designated IRB member has reviewed and accepted as satisfactory, the revised informed consent document *and* the written plan for informing currently enrolled subjects about the new risk.

Note that OHRP would not consider such suspensions of subject enrollment or of activities involving already enrolled subjects at the time of continuing review to be suspensions of IRB approval that needs to be reported to appropriate institutional officials, the head (or designee) of the agency conducting or supporting the research, and OHRP under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

I. What must the IRB records include regarding the documentation of conditions of IRB approval of research?

When the IRB approves research with conditions, the IRB must document, both to the investigator and in the IRB minutes for research reviewed at a convened meeting or elsewhere in the IRB records for research reviewed under an expedited review procedure, the following:

- (1) All conditions that must be satisfied by the investigator (45 CFR 46.102(h), 45 CFR 46.109(d), and 45 CFR 46.115);
- (2) The date when the IRB chairperson (and/or other individual(s) designated by the IRB) determines that all conditions of IRB approval have been satisfied, the date when initial approval becomes effective, and the date by which continuing review must occur;
- (3) In the case of initial review, any conditions under which some research activities may be initiated (for example, the investigator may initiate research in non-pregnant adults, but not in pregnant women or children); and
- (4) In the case of continuing review and the review of proposed changes to previously approved research, any conditions that need to be satisfied before an investigator can continue particular research activities related to those conditions (45 CFR 46.115(a)).

All correspondence between the IRB and the investigator regarding the conditions of approval set forth by the IRB must be maintained in the IRB records (45 CFR 46.115(a)(4)).

Copies of all research proposals reviewed by the IRB and approved sample consent documents, including any revised protocol or informed consent documents submitted by the investigator in order to satisfy the conditions of approval stipulated by the IRB, also must be maintained in the IRB records (45 CFR 46.115(a)(1)).

If you have specific questions about how to apply this guidance, please contact OHRP by phone at (866) 447-4777 (toll-free within the U.S.) or (240) 453-6900, or by e-mail at ohrp@hhs.gov.

PREGNANT WOMEN AND NEONATES IN RESEARCH

I. Informed consent requirements:

- a) Informed consent for research that involves pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates will be obtained from the mother and father (if necessary).
- b) According to Missouri State law (Chapter 431, Section 431.061), pregnant minors and/or mothers are considered legally capable of providing consent.

II. Research involving pregnant women or fetuses may only be approved if it meets all of the following Subpart B conditions (45 CFR 46.204):

- 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:
 - i. the prospect of direct benefit to the pregnant woman
 - ii. the prospect of a direct benefit both to the pregnant woman and the fetus, or
 - iii. 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, the woman's consent is obtained.

(OR – select either d or e)

- 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, 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 (d) or (e) above is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
- g) for children who are pregnant, assent and permission are obtained in accord with Subpart D for studies involving children;
- 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;
- j) individuals engaged in the research will have no part in determining the viability of a neonate.

III. One of the following Subpart B categories needs to be verbalized during the review and approval of a study involving neonates (viable neonates are subject to Subpart D):

45 CFR 46.205a: Neonates of uncertain viability and nonviable neonates may be involved 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 (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.

45 CFR 46.205b: Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research until the following additional conditions are met:

- 1) The IRB determined that: *(choose one or the other option)*
 - 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, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

45 CFR 46.205c: Nonviable neonates. After delivery nonviable neonate may not be involved in research until 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, except that the waiver and alteration provisions 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, 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 will not suffice to meet the requirements of this paragraph (c)(5).

IX. Research involving, after delivery, the placenta, the dead fetus, or fetal material (45 CFR 46.206):

- a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, is conducted 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 45 CFR 46 Subpart B are applicable.

PRISONERS IN RESEARCH

A prisoner is any individual confined or detained in a penal institution under a criminal or civil statute. This includes individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration. Individuals detained pending arraignment, trial, or sentencing are considered prisoners. Individuals not detained awaiting arraignment, trial, or sentencing are not considered prisoners.

I. When reviewing research that involves prisoners, including new submissions, continuing reviews, modifications and unanticipated problems, the IRB will meet the following specific requirements:

- 1) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
- 2) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is review by more than one Board only one Board need satisfy this requirement.

II. In the review of research involving prisoners, the IRB will consider the prisoner-specific definition of minimal risk (45 CFR 46.303(d)):

- 1) *Minimal risk* is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.
- 2) Note: *This means that when considering the risk a study poses to prisoner participants, the risk level should not be evaluated relative to the normal daily life of a prisoner. Risks should be evaluated relative to the normal daily life of a non-incarcerated individual.*

III. Research involving prisoners may only be approvable if (45 CFR 46.305):

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

- 1) The research is clearly deemed by this IRB to be under one of the permissible categories (under 46.306(a)(2) below).
- 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 about the study 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.

IV. Research involving prisoners must be certified to the Secretary as (45 CFR 46.306):

- 1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under 46.305 of this subpart; and
- 2) In the judgment of the Secretary the proposed research involves solely the following:
 - i. Study 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;
 - 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 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; or
 - 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. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

PRISONERS IN RESEARCH - EPIDEMIOLOGICAL RESEARCH WAIVER

- I. Research involving prisoners does not have to meet one of the four categories described in 46.306 if the sole purpose of the study is:**
 - To describe the prevalence or incidence of disease by identifying all cases, or
 - To study potential risk factor associations for disease.
 - The IRB approved the research in that it meets the requirements under III.(a)2-7 above for the approvability of research involving prisoners.
 - The IRB determined that the research presents no more than minimal risk and no more than inconvenience to the prisoner participants.
 - Prisoners are not a particular focus of the research.

- II. The range of studies to which the proposed waiver would apply includes epidemiological research related to chronic diseases, injuries, and environmental health. This type of research uses epidemiologic methods (such as interviews and collection of biologic specimens) that generally entail no more than minimal risk to the participants.**

ABBREVIATIONS

CIDER:	Clinical Investigational Data Exploration Repository
CFR:	Code of Federal Regulations
COI:	Conflict of Interest
DHHS:	Department of Health and Human Services
DMC:	Data Monitoring Committee
DRC:	Disclosure Review Committee
DSMB:	Data and Safety Monitoring Board
ED:	Emergency Department
FDA:	Food and Drug Administration
FWA:	Federal Wide Assurance
HDE:	Humanitarian Device Exemption
HIPAA:	Health Information Portability and Accountability Act
HRPO:	Human Research Protection Office
HUD:	Humanitarian Use Device
IBC:	Institutional Biosafety Committee
IAA:	IRB Authorization Agreement
IIA:	Individual Investigator Agreement
ICH/GCP:	International Conference on Harmonization/Good Clinical Practice
ICTS:	Institute of Clinical and Translation Sciences
IDE:	Investigational Device Exemption
IND:	Investigational New Drug
IO:	Institutional Official
IRB:	Institutional Review Board
NIH:	National Institutes of Health
NSR:	Non-Significant Risk (Device)
OHRP:	Office for Human Research Protections
PARC:	Protocol Adherence Review Committee
PHI:	Protected Health Information
PRMC:	Protocol Review and Monitoring Committee
RDRC:	Radioactive Drug Research Committee
SOP:	Standard Operating Procedures
SR:	Significant Risk Device