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Abbreviations

CFR:	Code of Federal Regulations
FDA:	Food & Drug Administration
HDE:	Humanitarian Device Exemption
HUD:	Humanitarian Use Device
IDE:	Investigational Device Exemption
IG:	Guide to Human Subjects Research
IND:	Investigational New Drug
IRB:	Institutional Review Board
NSR:	Nonsignificant Risk
OHRP:	Office for Human Research Protections
SOP:	UI IRB Standard Operating Procedures
SR:	Significant Risk
UI:	University of Iowa

Definitions – Glossary of Terms (Alphabetical)

Agent of the Organization – Agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility.

Chair – Chair or Vice-Chair, as designated on UI IRB roster submitted to OHRP, unless otherwise indicated.

Children (Child) –
DHHS definition: persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

FDA definition: persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted.

**For purposes of research conducted in Iowa, the term "child" as used in both the DHHS and FDA regulations is analogous to "minor" under Iowa Code and is viewed as "an unmarried person under the age of eighteen years." (Based on Iowa Code §600A.2 (13))

Clinical Investigation –
FDA definitions:
-any experiment that involves a test article and one or more human subjects and that is one of the following:

- subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or
- is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act but the results of which are intended to be submitted later to , or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.
- The term does not include experiments that are subject to the provision of 21CFR58, regarding nonclinical laboratory studies. (From 21 CFR 50.3(c); 21 CFR 56.102(c))

-any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. (From 21 CFR 312.3(b))

(Investigation): a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (From 21 CFR 812.3(h))

Clinical Trial – a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or

other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. (From 45 CFR 46.102(b))

Confidentiality – the ethical or legal right that information is considered private and will be held secret unless consent is provided permitting disclosure.

Conflict of Interest –
Conflict of interest exists when a researcher or an IRB member or a member of their immediate family has a significant financial interest related to a research project.

"Significant financial interest" means anything of monetary value or potential monetary value held by an investigator (and by the investigator's spouse and dependent children), and that reasonably appears to be related to the investigator's institutional responsibilities, as follows:

1. With regard to any publicly traded entity, remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000. [For purposes of the definition of "significant financial interest," remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship), equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value.]
2. With regard to any non-publicly traded entity, the value of any remuneration received from the entity in the calendar year preceding the disclosure, when aggregated, exceeds $5,000, or any equity interest (e.g., stock, stock option, or other ownership interest);
3. Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests; or
4. A position giving rise to a fiduciary duty, such as director, officer, partner, trustee, employee, or any position of management.
5. For investigators applying for or conducting research funded by the PHS, any reimbursed or sponsored travel related to the investigator's institutional responsibilities (i.e., travel is paid on behalf of the investigator and not reimbursed to the investigator so that the exact monetary value may not be readily available). Disclosure of this interest will include the purpose and duration of the trip, the identity of the sponsor/organizer, and the travel destination.

1. Has a signficant financial interest with either the sponsor of the study, or the company that makes any agent studied under a protocol. The current definition: UI Op Manual.

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

1. a member of the research team;
2. related to any member of the study team;
3. the faculty advisor of the PI/PD;
4. identified as "key personnel" on a funding mechanism that supports the research project; or
5. any other situation where the reviewer believes that another interest conflicts with his/her ability to deliberate objectively on a protocol.

For UI IRB members only, the following indicate a conflict of interest with a protocol under review:

- s/he serves as a co-investigator or other member of the research team or
- a member of his/her immediate family serves as a co-investigator or other member of the research team.

Immediate family means spouse or domestic partner, and dependent children.

Continuing Noncompliance – Any noncompliance that occurs repeatedly to the point of suggesting a pattern or an underlying problem. Continuing noncompliance may occur due to lack of knowledge (unintentional) or due to deliberate choice to ignore regulations or determinations of the IRB (intentional).

Covered Entity

A *covered entity* is:

1) a health plan
2) a health care clearinghouse (billing service)
3) a health care provider that transmits health information electronically

Existing (Data, Documents, Records, Pathological or Diagnostic Specimens) –

Existing with regards to these materials means the items must be “on the shelf” or in existence at the time the project is submitted to the IRB for review.

Federal Agency Other than DHHS that is subject to “The Common Rule”

Any one of the following:

- Agency for International Development (22 CFR 225)
- Central Intelligence Agency (Executive Order)
- Consumer Products Safety Commission (16 CFR 1028)
- Department of Agriculture (7 CFR 1c)
- Department of Commerce (15 CFR 27)
- Department of Defense (32 CFR 219)
- Department of Education (34 CFR 97)
- Department of Energy (10 CFR 745)
- Department of Homeland Security (Public law 108-458 Sec. 8306)
- Department of Justice (28 CFR 46)
- Department of Transportation (49 CFR 11)
- Department of Veteran’s Affairs (38 CFR 16)

- Environmental Protection Agency (40 CFR 26)
- Housing and Urban Development (24 CFR 60)
- National Aeronautics and Space Administration (14 CFR 1230)
- National Science Foundation (45 CFR 690)
- Office of Science and Technology Policy (Adoption of policy)
- Social Security Administration (Public law 7.5.26)

Guardian –
a person who is not the parent of a child, but who has been appointed by a court or juvenile court having jurisdiction over the child, to have a permanent self-sustaining relationship with the child and to make important decisions which have a permanent effect on the life and development of that child and to promote the general welfare of that child. A guardian may be a court or a juvenile court.

Unless otherwise enlarged or circumscribed by a court or juvenile court having jurisdiction over the child or by operation of law, the rights and duties of a guardian with respect to a child shall be as follows:

a. To consent to marriage, enlistment in the armed forces of the United States, or medical, psychiatric, or surgical treatment.
b. To serve as a guardian ad litem, unless the interests of the guardian conflict with the interests of the child or unless another person has been appointed guardian ad litem.
c. To serve as custodian, unless another person has been appointed custodian.
d. To make periodic visitations if the guardian does not have physical possession or custody of the child.
e. To consent to adoption and to make any other decision that the parents could have made when the parent-child relationship existed.
f. To make other decisions involving protection, education, and care and control of the child.

[From Iowa Code 232.2(21)]

Human subject –
Pre-2018 Regulations: a living individual about whom an investigator (whether professional or student) conducting research obtains a) data through intervention or interaction with the individual, or b) identifiable private information. (From 45 CFR 46.102.(d))

Revised Common Rule (9/21/2019): a living individual about whom an investigator (whether professional or student) conducting research:

i. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. (From 45 CFR 46.102(e)(1))

FDA definitions (human participant):
-an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A participant may be either a healthy human or a patient. (From 21 CFR 50.3(g))

-(Subject): a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control A subject may be in normal health or may have a medical condition. (From 21 CFR 812.3(p))

Identifiable Private Information -
Pre-2018 Regulations: private information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). This information is considered individually identifiable if the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (From 45 CFR 46.102(f)(2)

If information includes Protected Health Information (as defined later under Protected Health Information), identifiable information includes any of the following information for the individual, relative, employer, or household member of the individual:

- Name, street address, city, county, precinct, zip code, geocodes smaller than state
- Date of birth, ages > 89 years of age; or other dates such as diagnosis dates, procedure dates, admission or discharge dates
- Telephone numbers, fax numbers, e-mail addresses, social security numbers, medical record number
- Health plan beneficiary numbers, account numbers, certificate/license numbers
- Vehicle identifiers and serial numbers or license numbers, device identifiers and serial numbers
- Web URLs, Internet Protocol (IP) address numbers, biometric identifiers including finger/voice prints
- Full face photographic images and any comparable images.

Revised Common Rule (9/21/2019): private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (From 45 CFR 46.102(e)(5))

Identifiable Specimen – a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Interaction
An interaction includes communication or interpersonal contact between investigator and participant. (From 45 CFR 46.102(e)(3))

Intervention –
Pre-2018 Regulations: An intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the participant or the participant's environment that are performed for research purposes.

Revised Common Rule (9/21/2019): *Intervention* includes both physical procedures by which information or biospecimens are gathered (*e.g.,*venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (From 45 CFR 46.102(e)(2))

Legally authorized representative (LAR)-
Pre-2018 Requirements: an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

Revised Common Rule (9/21/2019): an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research. (From 45 CFR 46.102(i))

In studies involving children in the state of Iowa, the LAR is:

- the parent, OR
- the court-appointed guardian.

In studies involving cognitively impaired adults in the state of Iowa, the LAR is:

- the designated proxy (such as a Durable Power of Attorney for Health Care)
- the court-appointed guardian
- spouse
- adult child
- parent
- adult sibling.

In studies that involve cognitively impaired adults, permission must be sought from the first existing person in the above list, even if another relative is more conveniently available.

Minimal risk – the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily

life or during the performance of routine physical or psychological examinations or tests. (45 CFR 46.102(i) and 21 CFR 50.3(k))

In research involving prisoners – the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. (45 CFR 46.303(d))

Minor modifications – modifications to a research project and/or consent documents that pose no additional risk to subjects (e.g. changes in title, co-investigator(s), funding sources).If the modification is an addition or modification of procedures they must fall into one of the categories eligible for expedited review. To be considered a minor modification, it must also maintain similar or increased safeguards to protect the subject.

Noncompliance – failure to follow the federal regulations with respect to protection of human subjects in research or failure to follow the determinations of the IRB with respect to conduct of the research as approved by the IRB.

Nonscientist - an individual who has little or no formal scientific or medical training or experience.

Nonsignificant Risk (NSR) device investigation - one that does not meet the FDA definition for a Significant Risk study.

Privacy – freedom from unauthorized intrusion or the state of being let alone and able to keep certain personal information to oneself.

Private Information – includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.* medical record). (From 45 CFR 46.102(e)(4))

Protected Health Information (PHI) – information that:

1. is transmitted or maintained in any form (electronic, oral, paper) by a covered entity, and
2. identifies the individual or could reasonably be used to identify the individual; and
3. relates to the past, present or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present or future payment for the provision of healthcare to an individual.

(From 45 CFR 160.103)

Public Health Authority – an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with

such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate. (From 45 CFR 46.102(k))

Quorum – a majority of voting members of an IRB, including at least one member whose primary expertise is in a nonscientific area.

Research –
Pre-2018 Regulations: a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research even if they are a component of a larger non-research activity (e.g., instruction, demonstration.) (From 45 CFR 46.102(d))

Revised Common Rule (9/21/2019): a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:

1. Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
2. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions. (From 45 CFR 46.102(l))

Research Misconduct – fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the research community for proposing, conducting, or reporting research. It does not include honest

error or honest differences in interpretations or judgments of data or creative innovations that are nonetheless ethical, legal and meet professional standards.

Risk – the probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude may vary from minimal to significant.

Serious adverse drug experience– Any adverse drug experience (associated with the use of the drug) occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. (from 21 CFR 312.32(a))

Serious Noncompliance – Noncompliance that materially increases risks or that results in unexpected substantial harm to subjects or others. In addition the following instance(s) of noncompliance, as defined by OHRP, will always be determined as serious noncompliance:

- Non-Exempt human subjects research being carried out without IRB review and approval or without appropriate informed consent.
- Substantive modifications to IRB-approved research without IRB approval.

Significant Risk (SR) device study - one that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (From 21 CFR 812.3(m))

Suspension - By requirement of the convened IRB or an IRB Chair, a temporary halt to a selection of research activities being conducted under an IRB-approved project or a temporary halt to the IRB-approved project as a whole.

Termination - By requirement of the convened IRB, a permanent halt to some or all research activities in a previously approved IRB project.

Test Article – any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Federal Food Drug and Cosmetic Act, or under sections 351 or 354-360F of the Public Health Service Act. (From 21 CFR 50.3(j) and 21 CFR 56.102(l))

Unanticipated adverse device effect – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death the frequency, specificity or severity of which has not previously been identified in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (from 21 CFR 812.3(s))

Unanticipated problem involving risk to subjects or others –
Any problem or event that:

a) was not expected given the nature of the research, the population under study and the approved procedures or protocol for conduct of the study,
b) impacts the rights, safety, or welfare of subjects or others (e.g. those not directly involved in the research such as research staff or family members), and
c) is related to the research intervention, research procedures, and/or conduct of the research study.

Unexpected adverse drug experience– Any adverse drug experience (associated with the use of the drug), the frequency, specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information provided to subjects and the IRB. (from 21 CFR 312.32(a))

Vulnerable population - Federal regulations involving human subjects in research include specific protections for children, pregnant women and fetuses, and prisoners. In addition, the IRB expects the investigator to provide additional information regarding cognitively impaired individuals in research as well as indicate in the application any other populations that the investigator might consider to be particularly vulnerable in a research setting. Examples of these additional types of vulnerable populations include those persons who are educationally or economically disadvantaged, students, or other groups that may require special consideration.

Written or In Writing – refers to writing on a tangible medium (e.g., paper) or in an electronic format. (From 45 CFR 46.102(m))

A Summary of the Belmont Report
Ethical Principles & Guidelines for Research Involving Human Subjects

Reference: Federal Register. 1979 Apr 18;44(76):23192-7. Protection of human subjects: Belmont Report—ethical principles and guidelines for the protection of human subjects of research. U.S. Department of Health, Education, and Welfare.

Boundaries Between Practice & Research

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.

By contrast, the term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

Basic Ethical Principles

- **Respect for Persons**
- **Beneficence**
- **Justice**

Respect for Persons.
The principle of respect for persons divides into two separate moral requirements:

1. Individuals should be treated as autonomous agents, and
2. Persons with diminished autonomy are entitled to protection.

Application of this principle:
Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them.

Three elements of an informed consent process:

1. *Information* - The extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge.
2. *Comprehension* - The manner and context in which information is conveyed is as important as the information itself. Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability.
3. *Voluntariness* - An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence.

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:
(1) do not harm and
(2) maximize possible benefits and minimize possible harms.

In the case of particular projects, investigators and members of their institutions are obliged to ***give forethought to the maximization of benefits and the reduction of risk*** that might occur from the research investigation.

Application of this principle
Assessment of Risks and Benefits -- A method for determining whether the risks that will be presented to subjects are justified.

Elements of a Risk/Benefit Assessment:

1. The Nature and Scope of the Risks and Benefits –
   Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked. Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society).

2. The Systematic Assessment of Risks and Benefits --
   The idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible.

3. Assessment of the justifiability of research should reflect at least the following considerations
   (i) Brutal or inhumane treatment of human subjects is never morally justified.
   (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures.
   (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation).
   (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits.
   (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

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."

- The selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, 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.

Application of this principle
Selection of Subjects – moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Two levels of justice relevant to the selection of subjects:

1. Social -- Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.
2. Individual -- Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research.

Vulnerable subjects -- Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

Children in Research -- Codes

In general,when soliciting the assent of children, the PI should consider the age of the subjects, their maturity, and their ability to read and comprehend a written document in deciding how the assent will be obtained (e.g. verbally or written).

§46.404 {21 CFR 50.51}- Research not involving greater than minimal risk.

- *If the IRB finds that no greater than minimal risk to children is presented, approval may be given only if adequate provisions are made for soliciting the assent of the children and the permission of the parents or guardians. For this category of research, permission is required of each child's parents or guardians. Alternatively, the IRB may determine that the permission of one (1) parent/guardian is sufficient.*
- *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.*

§46.405 {21 CFR 50.52} - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

- *If the IRB finds that 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, approval may be given only if the IRB finds that:*
  - *a) the risk is justified by the anticipated benefit to the subjects, AND*
  - *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, AND*
  - *c) adequate provisions are made for soliciting the assent of the children and permission of the parents or guardians. For this category of research, permission is required of each child's parents or guardians. Alternatively, the IRB may determine that the permission of one (1) parent/guardian is sufficient.*

§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.

- *If the IRB finds that 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, approval may be given only if IRB finds that:*
  - *a) the risk represents a minor increase over minimal risk, AND*
  - *b) the intervention/procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations, AND*
  - *c) the intervention/procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or conditions, AND*
  - *d) adequate provisions are made for soliciting assent of the child and permission of BOTH parents/guardians unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has responsibility for the care and custody of the child;*

§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.

- *If the IRB does not believe the research meets the requirement of 404, 405, or 406, approval may be given 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 of DHHS, after consultation with a panel of experts in pertinent disciplines 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, OR
    2) 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 the research will be conducted in accordance with sound ethical principles and adequate provisions are made for soliciting the assent of children and the permission of both parents/guardians unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has responsibility for the care and custody of the child;.

§46.408 Requirements for permission by parents or guardians and for assent by children.

Assent of the 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.

In determining whether children are capable of assenting, the IRB shall take into account

- the ages,
- maturity, and
- psychological state of the children involved.

This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. ***§46.408(a)***

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented. ***§46.408(e)***

When can assent be waived (i.e.,the assent of the children is not a necessary condition for proceeding with the research):

If the IRB determines that

- the capability of some or all of the children is so limited that they cannot reasonably be consulted OR
- 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,

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 the conditions of the waiver of elements of consent as indicated in §46.116 of Subpart A. ***§46.408(a)***

Permission of each child's parents or guardian.

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.

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,
- one parent is unknown,
- one parent is incompetent,
- one parent is not reasonably available, OR
- when only one parent has legal responsibility for the care and custody of the child. ***§46.408(b)***

Permission by parents or guardians ***shall be documented*** in accordance with and to the extent required by §46.117 of subpart A. ***§46.408(d)***

When parental permission can be waived: ***§46.408(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 ***§46.408(b)***), 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.

NIH Certificate of Confidentiality

Certificates of Confidentiality

- Are ***issued by the National Institutes of Health (NIH)*** to protect the privacy of research subjects by protecting investigators and institutions from being compelled to release information that could be used to identify subjects with a research project.

- Are issued to institutions or universities where the research is conducted.

- The NIH automatically issues a Certificate of Confidentiality (COCs) for any NIH-funded project using identifiable, sensitive information. The CoC is issued as a term and condition of award. They do not issue a physical certificate.

- The IRB must agree the conditions of the Certificate of Confidentiality are met and documented appropriately in both the IRB application and Informed Consent Document.

- The NIH also considers requests for Certificates of Confidentiality for specific projects that are not funded by NIH, or other HHS agencies that issue Certificates. Such requests need to be submitted through the NIH online system in accordance with current NIH procedures for issuing Certificates.

- Allow the investigator and others who have access to research records ***to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or other proceedings***, whether at the federal, state, or local level. Identifying information in this context is broadly defined as any item or combination of items in the research data that could lead directly or indirectly to the identification of a research subject.

- Help achieve the research objectives and promote participation in studies by ***assuring privacy to subjects*** by protecting researchers and institutions from being compelled to disclose information that would identify research participants.

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

Examples of sensitive research activities include but are <u>not limited</u> to the following:
• Collecting genetic information;
• Collecting information on psychological well-being of subjects;
• Collecting information on subjects' sexual attitudes, preferences or practices;
• Collecting data on substance abuse or other illegal risk behaviors;
• Studies where subjects may be involved in litigation related to exposures under study (e.g., breast implants, environmental or occupational exposures).

Cognitively or Decisionally Impaired Individuals

Regulations

- *Unlike research involving children, prisoners, pregnant women, and fetuses, no additional Department of Health and Human Services (DHHS) regulations specifically govern research involving persons who are cognitively impaired.*

- While limited decision-making capacity should not prevent participation in research, it is important to keep in mind that additional scrutiny is warranted for research involving this population.

Assessing Capacity to Consent

- There are no generally accepted criteria for determining competence to consent to research for persons whose mental status is uncertain or fluctuating so the role of the IRB in assessing the criteria proposed by the investigator is of major importance.
- Refer to the document on the next page entitled "**Evaluation to Sign Consent**" for one option that may be used by investigator's to assess an individual's capacity to provide consent.
- Both IRBs and clinical investigators must keep in mind that decision making capacity may fluctuate, requiring ongoing assessment during the course of the research. The consent process should be ongoing.
- The IRB, at its discretion, may require an outside witness to observe the consent process.

Comprehension

- The determination of a subject's ability to understand the implications of the decision to participate in research is best made by the investigator.
- There is no universally accepted test or standard for making a determination of comprehension.
- This process should operate in research studies in much the same manner as the informed consent process in clinical treatment that does not involve research.

Voluntary Agreement

- Research should not be conducted against the wishes of the subject, and making certain that the written documents are indeed a reflection of reality is the function of the individual researcher and the IRB.

Second Signature on the Informed Consent Document

- The permission of another party is only required when the subject is determined to lack the legal ability to provide an informed consent.
- For information about who may provide consent for on behalf of an incompetent adult, refer to the Section in this Manual entitled "**Legally Authorized Representative.**"

HawkIRB Application Questions

- Section VI. Question 28
  Does this project involve cognitively impaired subjects?

- Section VI. Question 29.
  Describe how capacity to consent will be assessed.

- Section VI Question 30.
  Will you enroll subjects who do not have capacity to consent?

- Section VI Question 31
  Describe how you will assess/obtain assent from subjects who do not have capacity to consent

- Section VI. Question 32.
  Does this project involve subjects whose capacity to consent may change over the course of the study?

- Section VI. Question 33
  Describe how capacity to consent will be assessed throughout the conduct of the study including procedures when subject cannot continue to act on their own behalf.

- Section VI Question 34.
  Describe how you will continue to assess/obtain assent from subjects whose capacity to consent may change over the course of the study

- Section VI Question 35
  Describe procedures to ensure that the subject's representative is well informed regarding their role and obligations to protect the incompetent subject or person with impaired decision making capacity and how you will obtain consent of the legally authorized representative.

Evaluation to Sign an Informed Consent Document for Research

{DeRenzo EG, et al. J Health Care Law Polic 1998;1:66-87}

Subject Identifier: _____ Date of Evaluation: _____

Directions

Make a subjective judgment regarding item 1. Ask the subject questions 2-5 and record responses. The evaluator may use different wording in asking the questions in order to assist the subject's understanding.

1. Is the subject alert and able to communicate with the examiner? Yes ____ No ____

2. Ask the subject to name at least two potential risks of participating in the study.

_____

_____

3. Ask the subject to name at least two things that he/she will be expected to do during the study.

_____

_____

4. Ask the subject to explain what he/she would do if he/she no longer wanted to participate in the study.

_____

_____

5. Ask the subject to explain what he/she would do if he/she experienced distress or discomfort during the study.

_____

_____

Evaluator's Signature

It is my opinion that the subject is alert, able to communicate, and gave acceptable answers to the questions above.

_____ _____

Evaluator's Signature Date

Conflict of Interest Policy – IRB members

An IRB member **may not vote on a project** and is **not counted towards a quorum**, when a conflict of interest with the protocol exists. Below are the two types of conflict of interest that may occur:

Conflict of Interest in Research: The below exists whenever a reviewer (including UI IRB staff or consultants) or his/her immediate family (spouse or dependent children) has a significant financial interest related to a research project:

"Significant financial interest" means anything of monetary value or potential monetary value held by an investigator (and by the investigator's spouse and dependent children), and that reasonably appears to be related to the investigator's institutional responsibilities, as follows:

1. With regard to any publicly traded entity, remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000. [For purposes of the definition of "significant financial interest," remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship), equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value.]
2. With regard to any non-publicly traded entity, the value of any remuneration received from the entity in the calendar year preceding the disclosure, when aggregated, exceeds $5,000, or any equity interest (e.g., stock, stock option, or other ownership interest);
3. Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests; or
4. A position giving rise to a fiduciary duty, such as director, officer, partner, trustee, employee, or any position of management.
5. For investigators applying for or conducting research funded by the PHS, any reimbursed or sponsored travel related to the investigator's institutional responsibilities (i.e., travel is paid on behalf of the investigator and not reimbursed to the investigator so that the exact monetary value may not be readily available). Disclosure of this interest will include the purpose and duration of the trip, the identity of the sponsor/organizer, and the travel destination.

1. Has a signficant financial interest with either the sponsor of the study, or the company that makes any agent studied under a protocol. The current definition: UI Op Manual.

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

1. a member of the research team;
2. related to any member of the study team;
3. the faculty advisor of the PI/PD;
4. identified as "key personnel" on a funding mechanism that supports the research project; or
5. any other situation where the reviewer believes that another interest conflicts with his/her ability to deliberate objectively on a protocol.

Requirements for Informed Consent
{45 CFR 46.116}

- In general, no investigator may involve a human being as a subject in research covered under 45 CFR 46 or 21 CFR 50 unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

- An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

- The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

- No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Basic Elements of Informed Consent

In seeking informed consent the following information must 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;

   Note: FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study. (21CFR50.25(a)(5))

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

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

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

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

5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

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

The informed consent requirements are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

Nothing in the regulations is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law.

<u>Exception from prospective informed consent in the FDA Regulations</u>

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. 21 CFR 56.104(c)
2. Exception from Informed Consent Requirements for Emergency Research. 21 CFR 50.23 & 24.

Documentation of Informed Consent
{45 CFR 46.117}

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.

The consent form may be either of the following:

1) A written consent document that embodies the elements of informed consent required by 45 CFR 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 opportunity to read it before it is signed; (See Consent Elements above)

OR

2) A short form written consent document stating that the elements of informed consent required by 45 CFR 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 a 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 short form. (See the Section called “Non-English”)

<u>FDA difference regarding documentation</u>
FDA explicitly requires in 21CFR50.27(a), that consent forms be dated as well as signed by the subject or the subject’s legally authorized representative. HHS regulations do not explicitly require consent forms be dated.

§46.116(a) General Requirements for Informed Consent

(a) *General.* General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens. Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials is described in paragraph (e) of this section. General waiver or alteration of informed consent is described in paragraph (f) of this section. Except as provided elsewhere in this policy:

(1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.

(2) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.

(3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.

(4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

(5) Except for broad consent obtained in accordance with paragraph (d) of this section:

(i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

(ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

(6) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

§46.116(b) Basic Elements of Consent

(b) ***Basic elements of informed consent.*** Except as provided in paragraph (d), (e), or (f) of this section, in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:

(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 that 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 that may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

§46.116(c) Additional Elements of Consent

(c) ***Additional elements of informed consent.*** Except as provided in paragraph (d), (e), or (f) of this section, one or more of the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative'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 that may relate to the subject's willingness to continue participation will be provided to the subject;

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

(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (*i.e.,* sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

§46.117 Documentation of Informed Consent

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.

(b) Except as provided in paragraph (c) of this section, the informed consent form may be either of the following:

(1) A written informed consent form that meets the requirements of §46.116. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative.

(2) A short form written informed consent form 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, and that the key information required by §46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.

(c)(1) An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

(i) That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

(ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

(iii) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

(2) In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

Biennial Review

Annual Continuing Review is not required for:

- Most studies that qualify for the expedited review process *(45 CFR46.110).*
- Studies that have **completed subject intervention/interaction** and have indicated "closed to accrual."
- Studies that are limited to either **final analysis of identifiable data/biospecimens** or involve accessing follow-up clinical data from procedures that subjects undergo as part of clinical care.

*Eliminating continuing review for qualifying minimal-risk research reduces administrative burden for both the study team and IRB staff without impact to human subjects. To be eligible for this, the study cannot:

- Be subject to FDA oversight (involve an investigational drug or device)
- Be subject to the DOJ (Department of Justice)

NOTE: The IRB chair or their designee will issue an official "no annual continuing review required" determination for studies that qualify under this new policy. **For open studies, this will occur when the PI submits the next continuing review or modification submitted on or after January 21, 2019. The modification must be for research related changes and may not be submitted only to change the continuing review determination.** Continuing Reviews must be within 90 days of the next approval due by to be eligible for consideration for this pilot.

For eligible studies that do not require an annual continuing review, a ***Biennial check in*** will be required until the project is closed in HawkIRB by the Principal Investigator. The required Biennial check in will include a very brief, seven question check every two years. This review will be an administrative Human Subjects Office (HSO) review unless relevant information may be provided that would be subject to review by the IRB. The informed consent document and any IRB approved materials containing an IRB stamp will automatically update to the Biennial check in approval date.

Criteria for IRB Determination of expedited review of future Continuing Reviews

Expedited Review Category (8):

Under Category (8), an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **OR**

(b) Where no subjects have been enrolled and no additional risks have been identified; **OR**

(c) Where the remaining research activities are limited to data analysis.

Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

Expedited Review Category (9):

Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The determination that "no additional risks have been identified" does not need to be made by the convened IRB.

Criteria for IRB Determination of More than Annual Review

Except for studies determined to be exempt from IRB oversight, *all human subjects studies are subject to continuing review based on the level of risk as assessed by the board*.

- This review takes place ***at a minimum annually***, and may require more frequent review or reports as determined by the UI IRB.

- The length of approval is calculated from the date of the convened meeting at which the IRBs approve the protocol or approve the research with modifications.

- ***The appropriate length of approval should be considered as part of the full board discussion on both initial and continuing reviews.***

- Examples of when the IRB might consider requiring review more frequently than annually may include:

    1. Experimental therapies in which the clear potential for significant adverse experiences have been identified at the time of review;

    2. Non-therapeutic projects based on risk information provided at the time of initial review;

    3. Projects in which new information provided during the duration of the study (including at the time of continuing review) indicates a high probability of significant adverse experiences not previously reported;

    4. Projects in which local or outside adverse experience reports create new concerns regarding the need for closer project scrutiny;

    5. Projects where the UI IRB has concerns with regard to previous or potential serious or continuing noncompliance; or

    6. Other, as determined by the convened IRB.

In such cases, the IRB may consider granting approval:

- for time periods less than one year, or
- for a limited number of subjects over a period not to exceed one year, or
- with additional monitoring as a requirement.

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary of HHS has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it, as appropriate, after consultation with other federal departments and agencies and after publication in the FEDERAL REGISTER for public comment. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b)(1) An IRB may use the expedited review procedure to review the following:

(i) Some or all of the research appearing on the list described in paragraph (a) of this section, unless the reviewer determines that the study involves more than minimal risk;

(ii) Minor changes in previously approved research during the period for which approval is authorized; or

(iii) Research for which limited IRB review is a condition of exemption under §46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

(2) 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 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. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in §46.108(b).

(c) Each IRB that uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals that have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Frequently Asked Questions About Medical Devices

Additional copies are available from:

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January 2006

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Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors[1] Frequently Asked Questions About Medical Devices

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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.

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.

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.

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.

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/idepolcy.html

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.

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

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 <u>use</u> 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).

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.

- 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 alternatives 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/idepolcy.html

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/idepolcy.html

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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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.

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/cdrh/ode/blue-ide-d01-1.html

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

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)

- 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;

- 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

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

- 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

- 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

- 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

- Femoral, Jugular and Subclavian Catheters
- Hemodialyzers
- Hemofilters
- Implantable Electrical Urinary Incontinence Systems
- Implantable Penile Prostheses
- 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 ($\geq$ 28 days)
- Suprapubic Urological Catheters and accessories
- Urethral Occlusion Devices for greater than 14 days use
- Urethral Sphincter Prostheses
- 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 Prostheses
- 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

- 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

- 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)
- Keratoprostheses
- 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, perfluorpropane, 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 Prostheses (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."

Investigational Drug Treatment Studies – IND

IND – Investigational New Drug Application to the FDA

Investigational use suggests the use of an approved, marketed product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required.

The assessment of whether to require the investigator obtain an IND or to grant an FDA exemption from an IND is a critical IRB determination.

According to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;

(ii) it is not intended to support a significant change in the advertising for the product;

*(iii) **it does not involve a route of administration or dosage level, use in a subject 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) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];

(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and

(vi) it does not intend to invoke 21 CFR 50.24 (Exception from Informed Consent in Emergency Research).

There must be justification that there is no increase in risk or decrease in acceptability of risk. IRB should agree with the risk assessment provided by the investigator before granting an FDA exemption.

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)

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Revision 1

Guidance for Industry

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

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U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

Guidance for Industry[1] 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.

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.)).

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

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[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

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

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

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.

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:

- 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)).

Guidance for IRBs, Clinical Investigators and Sponsors

IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact CDER, Kevin Prohaska, (301) 796-3707, or CBER, Office of Communication, Outreach and Development, (301) 827-1800 or 1-800-835-4709, or CDRH, Linda Godfrey, (301) 796-5654.

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

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http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
Email: dsmica@cdrh.fda.gov
Fax: 301.847.8149
(Tel) Manufacturers Assistance: 800.638.2041 or 301.796.7100
(Tel) International Staff Phone: 301.827.3993

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Guidance for IRBs, Clinical Investigators, and Sponsors[1] IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed

This draft guidance, when finalized, will represent 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.

I. INTRODUCTION

FDA is issuing this guidance to remind institutional review boards (IRBs) of their longstanding role in the review of 1) the qualifications of the clinical investigator, 2) the adequacy of the facility in which the research will take place, and 3) the determination of whether an investigational new drug application (IND) or investigational device exemption (IDE) application is necessary for the proposed clinical investigation.

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.

To enhance human subject protection and reduce regulatory burden, the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This draft guidance document was developed as a part of these efforts and in consultation with OHRP.

II. BACKGROUND

Many of the recommendations in this guidance have appeared in other FDA guidance documents[2] or have been communicated to IRBs who have contacted the agency directly about

[1] This guidance has been prepared by FDA's Institutional Review Board Working Group, which includes representatives from FDA's Office of the Commissioner, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), and Office of Regulatory Affairs (ORA).

these issues.[3] FDA has also provided instructions to its field investigators on the types of documentation that should be reviewed during an IRB inspection to determine whether the IRB has established and followed its written procedures with respect to reviewing an investigator's qualifications, the adequacy of a site, and the determination of whether an IND or IDE is necessary.[4] FDA has compiled the advice from these various sources into this guidance to ensure that all IRBs have access to it. In addition, FDA provides guidance on how IRBs may efficiently fulfill these important responsibilities.

III. DISCUSSION

1. Must an IRB review the qualifications of clinical investigators who conduct FDA-regulated research?

Yes. Although FDA's regulations place responsibility on the sponsor to select clinical investigators who are "qualified by training and experience as appropriate experts" to investigate the test article,[5] IRBs also have a role in reviewing an investigator's qualifications.[6] The regulations at 21 CFR 56.107(a) require that an IRB be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. In addition, the regulations at 21 CFR 56.111 require that an IRB determine that the proposed research satisfies the criteria for approval, including that the risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to subjects. In order to fulfill these responsibilities, the IRB needs information about the qualifications of the investigator(s) to conduct and supervise the proposed research.

Depending upon the nature and risks of the proposed research and the relationship between the IRB and the investigator or the institution where the proposed research is being conducted, this may be relatively simple and straightforward or it may entail a more involved assessment.

In many cases, the IRB may have previous experience with an investigator or institution that would allow the IRB to readily determine that the clinical investigator is appropriately qualified to conduct and supervise the proposed research. In other cases, the IRB may need additional information; however, the IRB should be able to easily obtain a statement confirming the investigator’s qualifications from an administrator of the institution. For example, for proposed research to be conducted at a hospital where only credentialed hospital staff may conduct research, the IRB may be able to rely on another office at the institution (e.g., the credentialing

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[2] ICH E6 *Good Clinical Practice: Consolidated Guidance*, *3.1.3*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf; and FDA Guidance, *Using a Centralized IRB Review Process in Multicenter Clinical Trials*, Section IV (in relevant part, speaks to the "capacity of the institution to conduct or support the proposed research") http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127013.pdf.

[3] http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm.

[4] Compliance Program Guidance Manual (CPGM) 7348.809, Institutional Review Boards, November 28, 2011, generally, and Section III.J, K, and U.; http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133768.pdf.

[5] 21 CFR 312.53(a); see also 21 CFR 812.43(a).

[6] See 21 CFR 56.102(g), (h), and (j) for definitions of IRB, investigator, and sponsor, respectively; http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm.

office, the clinical investigator's medical department) for an assessment of the clinical investigator's qualifications. For proposed research to be conducted by a university faculty member (e.g., at an affiliated hospital or clinic), the IRB may be able to obtain a statement regarding the investigator's qualifications from the chair of the investigator's department.

On the other hand, if the reviewing IRB has no knowledge of either the clinical investigator or the institution (e.g., the IRB is not affiliated with the institution where the research will be conducted; the IRB has no previous experience with the investigator), the IRB would likely need to take additional steps to evaluate the investigator's qualifications (e.g., reviewing the curriculum vitae of the investigator, subinvestigators, and other necessary study staff; verifying professional associations and medical licensure; reviewing relevant publications).

The IRB may also need to assess the investigator's training and experience specifically related to the proposed study, particularly if the proposed research involves higher risks, vulnerable subjects, or novel technologies or surgical techniques. For such proposed research, the IRB's determination that the investigator is qualified may need to include a review of the investigator's previous specific experience both in this field (e.g., as demonstrated by recent presentations or publications), and prior experience with the test article. In addition, the IRB should pay particular attention to investigator's qualifications to conduct a study submitted for approval to the IRB if the study involves one or more of the following:

- a sponsor-investigator;[7]
- a study that is outside of the investigator's area of expertise; or
- any study design features or other characteristic(s) that may significantly increase potential risks to subjects.

The IRB may also elect to observe, or have a third party observe, the consent process and the research (21 CFR 56.109(f)), particularly if any concerns remain about the investigator's qualifications or experience.

Appropriately trained IRB support staff may assist in obtaining and assessing information about an investigator's qualifications. FDA recommends that the IRB's procedures describe the IRB's process for evaluating the investigator's qualifications to conduct and supervise the study.

2. Is any information publicly available from FDA about a clinical investigator's inspectional history?

Yes. IRBs may check the lists posted on FDA's website to determine whether a clinical investigator has been the subject of an inspection by the agency[8] and the results of such

[7] FDA's regulations (21 CFR 312.53(a) and 21 CFR 812.43(a)) require that a sponsor select clinical investigators who are "qualified by training and experience" to investigate the test article. In a sponsor-investigator (S-I) clinical trial, the S-I assumes the responsibilities of both the sponsor and the investigator (see 21 CFR 312.3(b) and 21 CFR 812.3(o)); therefore, there is no independent assessment of the clinical investigator's qualifications by the study sponsor. In this case, the IRB's review of the investigator's qualifications is particularly important to the determination that the risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to subjects.

inspections (e.g.,Warning Letters).[9] FDA also posts on its website a listing of all investigators who have been notified of the initiation of a disqualification proceeding[10] and a listing of all disqualified investigators.[11] FDA recommends that IRBs routinely check FDA's compliance and enforcement websites for information related to clinical investigator inspections and disqualification proceedings.

3. Must an IRB review the adequacy of the research site?

Yes. FDA's regulations require that before an IRB can approve research covered by the regulations, the IRB must be able to ascertain the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.[12] The regulations also require that each IRB have sufficient information to determine that the proposed research satisfies the criteria for approval.[13]

In the great majority of instances, an IRB will likely be familiar with the research site or institution at which the clinical investigator has proposed to conduct the research; in such cases, additional assessment of a site's adequacy will probably not be necessary (for example, if the research is to be conducted at the IRB's affiliated institution). In other cases, the IRB may need additional information in order to assess the site where the proposed research will take place to ensure it can adequately execute the protocol requirements. Depending upon the nature and risks of the proposed research and the IRB's prior knowledge of or relationship to the institution or other site at which the research will take place, this may be relatively simple and straightforward or it may entail a more involved assessment.

For example, if a proposed clinical investigation involves administration of medical procedures by qualified healthcare providers using medical equipment, the IRB should be prepared to assess the adequacy of the facility's staff and equipment, including the availability of emergency or specialized care if the need should arise. If the proposed research site is part of a major medical institution, the IRB would likely be able to simply note that fact. If, however, the IRB is unfamiliar with the proposed investigational site (e.g., research facility, hospital, physician's office, dental clinic), the IRB would likely need to confirm whether the site is appropriately staffed and equipped to conduct the proposed research. The IRB should be able to obtain a statement from an appropriate person or persons at the research site or institution stating that the facilities are adequate. Alternatively, the IRB could ask that the investigator provide a

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[8] Lists of investigators who have been inspected by FDA for CDER are posted at: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm; for CBER: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ucm165743.htm. Investigators who conducted a device study from 2009 to present are included in the Inspection Classification Database maintained by FDA's Office of Regulatory Affairs at: http://www.accessdata.fda.gov/scripts/inspsearch.

[9] See the agency's Electronic Reading Room, including Warning Letters (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm).

[10] See http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm092185.htm.

[11] See http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/ucm131681.htm.

[12] 21 CFR 56.107(a).

[13] 21 CFR 56.111(a).

description of the facility where the research will take place, including its staffing and resources relevant to the research under review.

4. What are the IRB's responsibilities with respect to verifying the determination of whether an IND or IDE is required for an FDA-regulated investigation?

The IRB's specific responsibilities vary, depending on the product that is the subject of the study; however, in general, the IRB should ask the investigator whether he/she considered the need to obtain an IND or IDE and the basis for any determination as to whether an IND/IDE is or is not needed.

Drug and Biologics Studies. FDA regulations require sponsors and clinical investigators to determine whether an IND is necessary for a particular study.[14] The sponsor (or sponsor-investigator of an individual investigator-initiated study) should be able to determine whether the IND regulations apply to a planned clinical investigation as required under 21 CFR 312.2(a). If a sponsor is uncertain, however, we recommend that the sponsor contact the appropriate review division (i.e., for the therapeutic area being studied) in the appropriate FDA Center for advice about whether the IND regulations apply (21 CFR 312.2(e)).

When reviewing a proposed study, IRBs should ask the clinical investigator whether an IND is or is not required and the basis for the determination. If the sponsor or investigator has determined that an IND is not needed, the IRB may request that the investigator provide a copy of any available documentation about the need for an IND (e.g., letter from the sponsor or FDA, other basis for that determination). If during its initial review of a study, the IRB questions whether an IND is necessary, but is unable to resolve this issue, the IRB should follow its procedures for resolving controverted issues (e.g., notifying the clinical investigator in writing of the IRB's concerns[15] and delaying approval of the study until the matter is resolved). FDA issued for public comment the *Draft Guidance for Industry: Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND.*[16] When finalized, the guidance will represent FDA's current thinking on this topic.

Organizational charts listing the review divisions for the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) and their phone numbers are available on FDA's website.[17] If the relevant review division is not known, the sponsor may contact CDER or CBER directly:

CDER: Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration

[14] See 21 CFR 312.2, 312.20, 312.50, and 312.60. Studies that are exempt from the IND requirements are required, however, to comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).
[15] 21 CFR 56.109(e)
[16] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf.
[17] CDER: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm;
CBER: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm.

10001 New Hampshire Avenue, 4th Floor
Silver Spring, MD 20993
(Tel) 301-796-3400

CBER: Office of Communication, Outreach and Development[18]
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800

Device Studies. The sponsor is responsible for determining whether submission of an IDE application to FDA is required before a study may proceed.[19] The IDE regulations (21 CFR 812) describe three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies.[20] SR device studies must have an IDE application approved by FDA before they proceed, and they must follow all of the IDE requirements.[21] NSR device studies must follow the abbreviated IDE requirements at 21 CFR 812.2(b) and do not require submission of an IDE application to FDA.

The sponsor is responsible for making the initial risk determination, SR or NSR, and presenting it to the IRB.[22] If the sponsor has determined that a device study is NSR, the IRB must review the sponsor's determination.[23] If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must inform the clinical investigator and, where appropriate, the sponsor.[24]

FDA is available to assist sponsors, investigators, and IRBs in making these determinations. For information on how to request such assistance, please see the guidance *Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices.*[25] Sponsors, clinical investigators, and IRBs who need assistance in making a risk determination for a medical device may also contact:

IDE Staff
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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[18] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm106001.htm.
[19] 21 CFR 812.2(b)(1)(ii).
[20] With the exception of 21 CFR 812.119, exempt studies are not subject to the IDE regulations. 21 CFR 812.2(c). Exempt studies are required to comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).
[21] 21 CFR 812.20(a)(1) and (2).
[22] 21 CFR 812.2(b)(1)(ii).
[23] 21 CFR 812.2(b)(1)(ii).
[24] 21 CFR 812.66.
[25] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126598.htm.

(Tel) 301-796-5640

Based on the information provided, FDA will determine if a device study is SR, NSR, or exempt from the IDE requirements found in 21 CFR Part 812. If FDA makes the SR or NSR determination for a study, the agency's determination is final. Additional information may be found in the *Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Device Studies.*[26]

Although not required by the regulations, FDA recommends that the IRB have written procedures that explain how the IRB makes a SR/NSR determination.

[26] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf.

Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

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)

December 2012
Drug Safety

Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

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Safety Reporting Requirements for INDs and BA/BE 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 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.

I. INTRODUCTION

This guidance is intended to help sponsors and investigators comply with the requirements for investigational new drug (IND) safety reporting and safety reporting for bioavailability (BA) and bioequivalence (BE) studies under 21 CFR 312.32, 312.64(b), and 320.31(d)(3). This document provides guidance to sponsors and investigators on expedited safety reporting requirements for human drug and biological products[2] that are being investigated under an IND and for drugs that are the subjects of BA and BE studies that are exempt from the IND requirements. This guidance defines terms used for safety reporting, makes recommendations on when and how to submit a safety report, and provides advice on other safety reporting issues that have arisen from sponsors and investigators.

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 AND BRIEF OVERVIEW OF THE REQUIREMENTS

On September 29, 2010, FDA published a final rule amending the IND safety reporting requirements under 21 CFR part 312 and adding safety reporting requirements for persons conducting BA and BE studies under 21 CFR part 320.

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[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in conjunction with the Center for Biologics Evaluation and Research (CBER) at FDA.

[2] For the purposes of this document, unless otherwise specified, all references to "drugs" or "drug products" include human drug products and biological products that are also drugs.

A. IND Safety Reporting Requirements

Under the former 21 CFR 312.32(c)(1)(i)(A) and (B), sponsors investigating a drug under an IND were required to notify FDA and all participating investigators, in a written IND safety report, of any adverse experience associated with the use of the drug that was both serious and unexpected, and any finding from tests in laboratory animals that suggested a significant risk for human subjects. The phrase *associated with the use of the drug* was defined as "there is a reasonable possibility that the experience may have been caused by the drug" (former 21 CFR 312.32(a)). Notwithstanding this definition, sponsors frequently reported, as individual cases, serious adverse experiences for which there was little reason to believe that the drug caused the event. For example, sponsors often reported:

- Serious adverse experiences (e.g., mortality or major morbidity) that were likely to have been manifestations of the underlying disease
- Serious adverse experiences that commonly occurred in the study population independent of drug exposure (e.g., strokes or acute myocardial infarctions in an elderly population)
- Serious adverse experiences that were study endpoints (i.e., the study was evaluating whether the drug reduced the rate of these events)

These types of reports are generally uninformative when reported as single events (i.e., without a comparison of the incidence of the event in treated and untreated subjects), and they do not contribute meaningfully to the developing safety profile of an investigational drug or to human subject protection. Attempting to review and evaluate these reports without the necessary context was also a drain on resources for FDA, investigators, and institutional review boards (IRBs),[3] diverting them from other activities.

The tendency for sponsors to report such uninformative individual cases seems to have been primarily related to interpretation of the *reasonable possibility* standard in the definition of *associated with the use of the drug*. For an individual case of the types of adverse events described above, there would generally not be enough evidence to suggest that there was a reasonable possibility that the drug caused the adverse event. Such events would therefore not meet the definition of "associated with the use of the drug" and should not have been reported as IND safety reports.

Under 21 CFR 312.32, the amended requirements revise the definitions used for safety reporting and make clear when to submit expedited safety reports. The requirements distinguish circumstances in which it is appropriate to submit individual cases and circumstances in which cases should be aggregated and compared to cases in a control group and submitted only if the event occurs more frequently in the drug treatment group. Compliance with these requirements will increase the likelihood that submitted information will be interpretable and will meaningfully contribute to the developing safety profile of the investigational drug and improve the overall quality of safety reporting. In addition, reducing the number of uninformative individual reports will enhance the ability of sponsors, FDA, investigators, and IRBs to focus on safety issues that affect public health.

[3] See section VI.F of this guidance for more information on safety reporting to IRBs.

Because the regulations require reporting certain adverse events in the aggregate rather than as individual cases, it is important for sponsors to collect and evaluate safety data systematically during product development, including accumulating safety data (see section V.A.3).

B. Safety Reporting Requirements for BA and BE Studies (21 CFR 320.31(d)(3))

Under former 21 CFR 320.31(d), certain in vivo BA and BE studies in humans were exempted from the IND requirements under part 312 if specific conditions were satisfied (i.e., samples of any test article and reference standard were reserved by the persons conducting the study and released to FDA upon request, studies were conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and informed consent set forth in 21 CFR part 50). Although these studies were not subject to the IND safety reporting requirements under 21 CFR 312.32, FDA received safety information from these studies that provided important information about drugs under investigation. For this reason, the final rule contains safety reporting requirements under 21 CFR 320.31(d)(3) for persons conducting BA or BE studies that are exempt from the IND requirements. These requirements will help FDA monitor the safety of these drugs and better protect human subjects enrolled in BA or BE studies.

III. DEFINITIONS (21 CFR 312.32(a))

The IND safety reporting rule introduces terms and definitions that are meant to be clear and consistent. New definitions replace the definition of the phrase *associated with the use of the drug* in former 21 CFR 312.32(a), which, as previously discussed, has been a source of confusion. The definitions, followed by further explanation and examples, are provided in this section, and Appendix A provides a visual representation of the relationship between three of the terms.

A. Adverse Event (21 CFR 312.32(a))

> Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

B. Suspected Adverse Reaction (21 CFR 312.32(a))

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Within the reporting requirement under 21 CFR 312.32(c)(1)(i), FDA makes clear the meaning of *reasonable possibility* by providing the following examples of types of evidence that would suggest a causal relationship between the drug and the adverse event.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event. We consider the application of the *reasonable possibility* causality standard to be consistent with the discussion about causality in the International Conference on Harmonization (ICH) E2A Guideline ("ICH E2A guidance").[4] However, the Agency notes there is a difference between this rule and the ICH E2A guidance with respect to who is responsible for making the causality judgment. The sponsor is responsible for making the causality judgment for this rule, whereas the ICH E2A guidance recommends that the judgment be based on either the investigator's or the sponsor's opinion. This is explained further in sections V.A and VI.D.1 of this document.

[4] *ICH E2A Guideline for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, March 1995, pages 6-7. CDER guidance documents can be found on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web site. CBER guidance documents can be found at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

C. Adverse Reaction[5]

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

D. Unexpected (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

This definition relies entirely on the adverse events or suspected adverse reactions listed in the investigator brochure for the particular drug under investigation (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is *unexpected*.[6] This means that events not listed for the particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for IND safety reporting purposes. In the clinical trial setting, there has been some confusion with the term "expected" as it has been used to mean "anticipated" for the disease being treated or population being studied rather than "listed in the investigator brochure." For example, some adverse events can be anticipated to occur as a result of a disease or in an older population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not "expected" because they are not listed in the investigator brochure (i.e., the test drug is not suspected or known to cause them). Monitoring and reporting these types of anticipated events are further discussed in section V.A.3 of this document.

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[5] For the purposes of prescription drug labeling, the term *adverse reaction* is defined to mean "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event" (see 21 CFR 201.57(c)(7) and 201.80(g)).

[6] For drugs marketed or approved in the United States, ordinarily FDA-approved prescription drug labeling is used as the basis for determining whether an event is unexpected for reporting purposes.

Adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes until it is included in the investigator brochure as occurring with the drug under investigation.

E. Serious (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

This definition permits either the sponsor or the investigator to decide whether an event is *serious*. The investigator's perspective may be informed by having actually observed the event, while the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. Because serious adverse events are critically important for the identification of significant safety problems, FDA believes taking into account both the investigator's and the sponsor's assessment is important. Therefore, if either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

We note that the definition of "serious" differs slightly from the ICH E2A guidance[7] (i.e., FDA definition uses "and" rather than "or" in the sentence "Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject ***and*** may require medical or surgical intervention to prevent one of the outcomes listed in this definition"). We will accept application of either the FDA definition (i.e., "and") or the ICH E2A guidance criteria (i.e., "or") in determining the seriousness of an event.

[7] *ICH E2A*, pages 4-5.

F. Life-Threatening (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

As with the definition of *serious,* the determination of whether an adverse event is life-threatening can be based on the opinion of either the investigator or sponsor. Thus, if either believes that it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes (21 CFR 312.32(a)).

IV. REVIEW OF SAFETY INFORMATION (21 CFR 312.32(b))

The sponsor is required to review promptly all information relevant to the safety of the drug (21 CFR 312.32(b)). During the course of drug development, adverse event information is generally reported to a sponsor by investigators conducting clinical trials; however, a sponsor may become aware of new safety information from a variety of sources, both domestic and foreign. Some examples of sources are listed as follows, but safety information from any other source would also need to be reviewed and evaluated by the sponsor.

- Animal studies or in vitro studies
- Clinical or epidemiological investigations
- Reports in the scientific literature
- Unpublished scientific papers
- Information presented at scientific meetings
- Reports from foreign regulatory authorities
- Reports from commercial marketing experience
- Safety information presented at a professional meeting
- Foreign spontaneous reports

The sponsor's review should include examining data from all sources and deciding whether the information meets the criteria for expedited reporting (see section V), as well as evaluating all accumulating data at regular intervals to update safety information and to identify new safety signals. Some types of information should be sought by the sponsor as part of its continuous pharmacovigilance on the safety of the drug. For example, the sponsor should conduct literature searches regularly with a frequency appropriate to the drug or study design to seek safety information and report that information if necessary.

V. MONITORING THE SAFETY DATABASE AND SUBMITTING IND SAFETY REPORTS

Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in an IND safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information

qualifies for reporting (see VII.C for a discussion of IND safety reporting time frames). *Participating investigators* include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1)). This includes, for example, all investigators participating in clinical trials under an IND, at U.S. and non-U.S. sites, for the investigational drug, and any investigators conducting a study under their own IND for whom the sponsor provides investigational drug.

In addition, the sponsor must identify in each IND safety report all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information (21 CFR 312.32(c)(1)). The analysis must include similar reports from all INDs held by the sponsor and any other relevant information known to the sponsor (21 CFR 312.32(c)(1)). Sponsors should evaluate a suspected adverse reaction in the context of other related reports or adverse events, including those that occurred in the placebo or active comparator group and those that occurred in pre- and postmarketing studies.

Sponsors should conduct ongoing safety evaluations, including periodic review and analyses of their entire safety database, not only for IND safety reporting purposes, but also to update investigator brochures, protocols, and consent forms with new safety information (see section VI.B.2 for information about updating investigator brochures).

Sponsor-investigators, as defined in 21 CFR 312.3(b), are required to comply with both the sponsor and the investigator responsibilities under 21 CFR part 312. With respect to safety reporting under 21 CFR 312.32, this includes examining data from reports in the scientific literature and reports from foreign commercial marketing experience. The Agency recognizes that a sponsor-investigator may not have access to complete safety data maintained by a commercial sponsor or other sponsor-investigators, but sponsor-investigators are responsible for evaluating all safety information available to them. To protect human subjects, we recommend that entities that provide drug to or receive drug from other entities share safety information with each other.

The sponsor must submit an IND safety report when any of the following criteria are met:

A. Serious and Unexpected Suspected Adverse Reaction (21 CFR 312.32(c)(1)(i))

The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- *Suspected adverse reaction*
- *Serious*
- *Unexpected*

If the adverse event does not meet all three of the definitions, it should not be submitted as an IND safety report.[8]

Deciding whether the adverse event meets the definition of a *suspected adverse reaction* is usually the most difficult determination, but this decision is critical to avoid the submission of uninformative IND safety reports. The sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a *suspected adverse reaction*. The suspected adverse reaction must then be reported expeditiously in an IND safety report if it also meets the definitions of *serious* and *unexpected* (21 CFR 312.32(c)(1)(i)).

Under 21 CFR 312.64, investigators are required to provide a causality assessment for each serious adverse event reported to the sponsor. For serious events that are unexpected, the sponsor considers the investigator's causality assessment but submits an IND safety report only for those events for which the sponsor determines there is a reasonable possibility that the drug caused the event, regardless of the investigator's causality assessment. (See Appendix B for a chart that clarifies sponsor and investigator responsibilities for reporting.)

For example:

- Sponsor would not report events for which the investigator's assessment is positive for causality, but where the sponsor's evaluation did not find evidence to suggest a causal relationship between the drug and the event.
- Sponsor would report events for which the investigator's assessment is negative for causality, but where the sponsor's evaluation found evidence to suggest a causal relationship between the drug and the event.

The investigator's assessment of causality should be included in the report submitted to the sponsor. If the investigator fails to provide a causality assessment and the sponsor is unable to obtain it, or if the investigator assesses the causality as unknown, the sponsor should evaluate the event without the investigator's assessment.

To assist sponsors with determining whether an adverse event meets the definition of suspected adverse reaction, the requirement under 21 CFR 312.32(c)(1)(i) specifies that sponsors are to report to FDA ***only*** if there is evidence to suggest a causal relationship between the drug and the adverse event and it provides examples of such evidence, described below.

1. Individual Occurrences (21 CFR 312.32(c)(1)(i)(A))

Certain serious adverse events are informative as single cases because they are uncommon and are known to be strongly associated with drug exposure. Some examples include angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome. The occurrence of even one case of such adverse events

[8] Adverse events that do not meet the criteria for reporting in an IND safety report must still be reported in accordance with the periodic reporting regulations, when applicable (e.g., 21 CFR 312.33 IND annual report).

would meet the definition of *suspected adverse reaction* (i.e., there is a reasonable possibility that the drug caused the event).

2. One or More Occurrences (21 CFR 312.32(c)(1)(i)(B))

A single occurrence, or a small number of occurrences, of a serious adverse event that is uncommon in the study population, but not commonly associated with drug exposure may also be informative. If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive to report in an IND safety report. Often, more than one occurrence from one or multiple studies would be needed before the sponsor could determine that there is a *reasonable possibility* that the drug caused the event. Examples include tendon rupture or heart valve lesions in young adults, or intussusception in healthy infants.

3. Aggregate Analysis of Specific Events (21 CFR 312.32(c)(1)(i)(C))

Certain serious adverse events can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population). An example of the former would be a non-acute death observed in a trial in cancer patients. An example of the latter would be an acute myocardial infarction observed in a long-duration trial in an elderly population with cancer. Although these serious adverse events meet the definition of *unexpected* at 21 CFR 312.32(a), as they are not listed in the investigator brochure (see sections III.D and VI.B), these events do not warrant expedited reporting as individual cases because it is not possible, based on a single case, to determine that there is a reasonable possibility that the drug caused the event. As a result, they do not meet the definition of a suspected adverse reaction.

Section 312.32(c)(1)(i)(C) requires reporting in an IND safety report when an aggregate analysis of specific events observed in a clinical trial indicates those events occur more frequently in the drug treatment group than in a concurrent control group. In cases where a randomized comparison is not available, the estimate of whether the rate is greater than in a control population would have to be based on some other group not receiving the drug, such as the general population or populations similar to the drug population with respect to demographics and disease state but not receiving the test drug (e.g., a historical control). An aggregate analysis of specific events should reflect information from all relevant studies. Therefore, it should be performed both for individual studies (if there are enough events to be informative) and across all studies, including across INDs of the drug, to determine whether they meet the criteria for expedited reporting.

The following recommendations are intended to assist sponsors with protocol development and monitoring the safety database.

a. Reporting Study Endpoints (21 CFR 312.32(c)(5))

Generally, study endpoints refer to outcomes that sponsors are measuring to evaluate efficacy. For trials designed to evaluate the effect of a drug on disease-related mortality or major morbidity, endpoint information should be collected, tracked, and monitored, usually by a Data Monitoring Committee (DMC), during the course of the study. The protocol would prespecify a monitoring plan for determining whether subjects receiving the drug treatment are at higher risk for the outcome (e.g., all-cause mortality), and such results would be reported according to the protocol. The study endpoints must be reported to FDA by the sponsor according to the protocol, and ordinarily would not be reported as IND safety reports, except when there is evidence suggesting a causal relationship between the drug and the event (21 CFR 312.32(c)(5)). For example, a death ordinarily would not be reported as an individual case in an expedited report from a trial designed to compare all-cause mortality in subjects receiving either drug treatment or a placebo. On the other hand, in the same trial with an all-cause mortality endpoint, if the death occurred as a result of an anaphylactic reaction that coincided with initial exposure to the drug, or as a result of fatal hepatic necrosis, the death must be reported as an individual case in an IND safety report because there would then be evidence suggesting a causal relationship between the drug and the event (21 CFR 312.32(c)(5)).

In addition to the study endpoints described above, some studies also evaluate the effect of the drug on several other specific adverse events, often called "safety endpoints" or "secondary endpoints." These safety endpoints or secondary endpoints should be identified in the protocol and monitored and reported by the sponsor as described in section V.A.3.b.

b. Serious Adverse Events That Are Not Study Endpoints

Other serious adverse events that are not study endpoints and are not "expected" (e.g., because they are not in the investigator's brochure), can be anticipated to occur with some frequency during the course of the trial, regardless of drug exposure, depending on the patient population and disease under study. Examples of such "anticipated" events include known consequences of the underlying disease or condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline. In general, a limited number of occurrences of such an adverse event in a study population in which occurrences of the event are anticipated is not an adequate basis to conclude that the event is a suspected adverse reaction (i.e., that there is a reasonable possibility that the drug caused the event). Such events should not be reported individually as they occur because they are uninformative as single cases. Such anticipated adverse events should nonetheless be monitored at appropriate intervals, and the numbers of events in each arm of a controlled study should be compared. The adverse event must be reported to FDA expeditiously as an IND safety report if there is an imbalance between arms suggesting there is a reasonable possibility that the drug

caused the adverse event (21 CFR 312.32(c)(1)(i)(C)). It is important to consider the entire clinical trial database in such analyses.

i. Identifying and monitoring protocol-specified serious adverse events

At the time of protocol development, the sponsor should identify in the protocol the serious adverse events that it does not plan to report individually in an expedited manner because they are anticipated to occur in the study population at some frequency independent of drug exposure. It is not possible or desirable to list in the protocol every adverse event that may occur in the study population. Factors to consider when deciding which adverse events to identify include, for example, characteristics of the study population, natural progression of the disease, background event rates, background regimens, co-morbid conditions, and past experience with similar populations. The list of the more common serious adverse events, based on past experience, could be used for all protocols (taking into account population differences) because the analyses of these adverse events should consider the entire safety database. Therefore, the sponsor should limit the list to those events that are common enough to make an overall analysis useful. For example, in a long-term osteoporosis trial in an elderly population, it would be reasonable to list myocardial infarction, but unreasonable to list acute narrow angle glaucoma, an event that can occur in this elderly population, but is relatively rare. The protocol should also describe how the protocol-specified serious adverse events will be monitored. The sponsor or an independent group should monitor the identified events during the conduct of the trial and submit an IND safety report if an aggregate analysis indicates that the events are occurring more frequently in the drug treatment group (see section V.A.3.c).

ii. Reporting serious adverse events that are not protocol-specified

The fact that an event is not identified in the protocol does not mean that the sponsor must report a single occurrence of the event expeditiously. The sponsor should use judgment in determining whether there is a reasonable possibility that the drug caused the event. Often, a single case will be unpersuasive. For example, in the osteoporosis trial previously described, a single case of acute narrow angle glaucoma would generally not be reported in an IND safety report because such cases are seen in an untreated elderly population, but if monitoring for subsequent cases revealed additional cases in the drug treatment group, the sponsor would consider the events to meet the definition of suspected adverse reactions at 21 CFR 312.32(a) and would report them expeditiously. However, FDA will accept expedited reports for individual cases of unexpected serious adverse events that are not study endpoints and are not specified in the protocol as "anticipated" (e.g., they are known consequences of the disease being treated or common in the study population) to address concerns expressed by sponsors about not expeditiously reporting such cases.

c. Safety Surveillance for Ongoing Clinical Trials[9]

Because it is critical that a drug product's risks be adequately assessed during development, sponsors should ensure that they have in place a systematic approach for safety surveillance. Such an approach should include a process for reviewing, evaluating, and managing accumulating safety data from the entire clinical trial database at appropriate intervals. In some cases, a specific independent committee with substantial external representation could be created to perform this function. In others, the sponsor may choose to create a safety team within the sponsor's organization. In either case, this independent group would oversee the evolving safety profile of the investigational drug and evaluate, at appropriate intervals, the accumulating data from individual and multiple clinical trials, as well as other available information.

B. Findings From Other Sources (21 CFR 312.32(c)(1)(ii) and (iii))

The sponsor must also report expeditiously any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug (21 CFR 312.32(c)(1)(ii) and (iii)). These reports are required for studies from any source, regardless of whether they are conducted under the IND or by the sponsor (21 CFR 312.32(c)(1)(ii) and (iii)). A finding that suggests a *significant risk* would ordinarily result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation. For example, actions often taken in response to a significant risk finding include immediate revision of the informed consent, intensification of subject monitoring, revised eligibility criteria or screening procedures, enrollment hold, or consideration of discontinuation of the trial. The sponsor is also required to submit protocol amendments that describe changes to the protocol or other documents (21 CFR 312.30(b)) in addition to the IND safety report.

1. Findings From Other Studies (21 CFR 312.32(c)(1)(ii))

Findings that suggest a significant risk generally arise from ongoing or completed clinical studies, pooled data from multiple studies, epidemiological studies, and published and unpublished scientific papers. Findings from clinical studies that are subject to this requirement are those that have not already been reported under 21 CFR 312.32(c)(1)(i). For example, any clinically important finding from a drug interaction study, from a study evaluating the QT interval, or from a study of a marketed drug would be reported under this provision. An example of such a finding would be a prolongation of the QT interval in subjects receiving the investigational product.

[9] For more discussion of this subject, see FDA's guidances on *Establishment and Operation of Clinical Trial Data Monitoring Committees* and *Premarketing Risk Assessment* (see footnote 4 for location), and references 1-3.

2. Findings From Animal or In Vitro Testing (21 CFR 312.32(c)(1)(iii))

Findings from animal studies, such as carcinogenicity, mutagenicity, teratogenicity, or reports of significant organ toxicity at or near the expected human exposure are examples of the types of findings that could suggest a significant risk. Before reporting a finding to FDA, the sponsor should use judgment to decide whether the finding suggests a significant risk in humans or is too preliminary to interpret without replication or further investigation.

C. Increased Occurrence of Serious Suspected Adverse Reactions (21 CFR 312.32(c)(1)(iv))

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (21 CFR 312.32(c)(1)(iv)). A baseline incidence rate may not always be available, but when one is available or can be inferred from data or analyses in the investigator brochure (e.g., from a table), a clinically important increase from that rate must be reported (21 CFR 312.32(c)(1)(iv)). The decision about when to report is a matter of judgment based on a variety of factors including the study population, the nature and seriousness of the reaction, and the magnitude of the observed increase in the rate. For example, rhabdomyolysis is a recognized, infrequent adverse reaction that is known to occur in the HMG-CoA reductase inhibitor class of drugs (i.e., statins). A higher than expected rate would merit reporting.

VI. OTHER SAFETY REPORTING ISSUES

A. Alternative Reporting Arrangements (21 CFR 312.32(c)(3))

Title 21 of the CFR §§ 312.32(c)(1) and 312.32(c)(1)(v) specify the format and time frame for reporting suspected adverse reactions in an IND safety report (see section VII). Sponsors may request and adopt different reporting formats or frequencies if agreed to in advance by the director of the FDA review division that has responsibility for review of the IND (21 CFR 312.32(c)(3)). In addition, FDA may require a sponsor to submit IND safety reports in a different format or at a different frequency than required under 21 CFR 312.32(c)(1) and 312.32(c)(1)(v) (see 21 CFR 312.32(c)(3)). FDA may require a sponsor to continue to report expeditiously a medically significant suspected adverse reaction that is listed in the investigator brochure as observed with the drug (i.e., expected) so that its rate can be carefully monitored (21 CFR 312.32(c)(3)). For example, if a single occurrence of Stevens-Johnson Syndrome was observed in a subject receiving the investigational drug, FDA may require expedited reporting of additional cases of rash of a lesser severity. FDA may also require an alternative format or frequency for reporting suspected adverse reactions from clinical trials once a study or design has been identified as posing a potential or previously unforeseen risk to participants. See sections VI.D and VI.D.3 for information on investigator reporting arrangements.

B. Investigator Brochure

The purpose of the investigator brochure is to provide the investigator with information (clinical and nonclinical) about the investigational drug that is relevant to the study of the drug in human subjects. The investigator brochure should include the information that is important for the investigator, who is administering the drug to human subjects, to know and understand. The investigator brochure is required to include information about the following (see 21 CFR 312.23(a)(5)):

- Drug substance and formulation
- Pharmacological and toxicological effects of the drug in animals (and in humans, if known)
- Pharmacokinetics and biological disposition of the drug in animals (and in humans, if known)
- Information relating to safety and effectiveness in humans obtained from prior clinical studies
- Information about possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs
- Precautions or special monitoring to be done as part of the investigational use of the drug

The Agency accepts a variety of formats for the investigator brochure. Although the most important purpose of the investigator brochure is to provide the investigator with information about the investigational product, the investigator brochure is also used by the sponsor as the basis for determining whether a suspected adverse reaction is *unexpected* for purposes of IND safety reporting (see section III.D).

1. Clinical Risk Information

With respect to clinical risk information, the investigator brochure should specifically and accurately list those adverse events that have been observed with an investigational drug and for which a causal relationship with the drug is suspected or confirmed. In addition, the investigator brochure should list adverse events that commonly occur with the class of drugs or may be predicted to occur based on the pharmacological properties of the drug, even if not yet observed with the drug under investigation, to alert the investigator to the possibility of their occurrence. Sponsors should use judgment in determining which terms accurately reflect a particular adverse event, including syndrome names if applicable. The investigator brochure should not list adverse events that are unlikely to have been caused by the drug because such lists could dilute the importance of clinically meaningful risk information.

2. Updating the Investigator Brochure

During the course of the clinical trial, the sponsor must update the investigator brochure on an ongoing basis with new important safety information (21 CFR 312.55). Some updates to the investigator brochure should be made as soon as possible while others can be made on a routine basis. For example, a new safety finding that represents a

significant risk to study subjects (e.g., a finding that patients with renal impairment are likely to experience a serious adverse reaction) should be communicated to investigators immediately, along with an update to the investigator brochure and possibly to the protocol (e.g., a change in screening procedures and eligibility criteria). On the other hand, an update to reflect a minor change in a suspected adverse reaction rate could be done on an annual basis.

The sponsor should exercise judgment when deciding whether the threshold has been reached for adding a newly observed adverse event to the investigator brochure. Criteria to consider usually include the strength of the evidence from individual or multiple cases and previous knowledge about the drug or drug class.

Until the investigator brochure is updated to include a new serious, suspected adverse reaction, subsequent occurrences of similar serious, suspected adverse reactions must be submitted expeditiously in IND safety reports (21 CFR 312.32(c)(1)(i)) to FDA and all participating investigators.

There is more than one acceptable approach for updating the investigator brochure with new safety information. For example, adding a new serious and unexpected suspected adverse reaction to the investigator brochure as an addendum, rather than reissuing the entire brochure, is an acceptable approach for keeping investigators informed of new observations. Sponsors should ensure that any addenda are incorporated into the next full revision of the investigator brochure.

C. Unblinding

The blind should ordinarily be broken for IND safety reports submitted to FDA and all participating investigators. Knowledge of the treatment received is necessary for interpreting the event, may be essential for the medical management of the subject, and may provide critical safety information about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). The Agency does not believe that unblinding single or small numbers of serious and unexpected adverse event cases will compromise the integrity of the study, in part because such unblinding should be infrequent. For example, because the requirement under § 312.32(c)(5) specifically describes different reporting requirements for study endpoints, in a trial evaluating death, myocardial infarctions, and strokes as endpoints, a case of liver injury, if unblinded, would have no effect on overall study integrity.

In general, if the blind is broken and a subject with an adverse event that would meet the criteria for reporting as a single event was receiving placebo, the event should not be reported in an IND safety report because there is not a reasonable possibility that the drug caused the adverse event. If the blind is broken and this subject was receiving drug treatment (test drug or active comparator), it must be reported in an IND safety report (21 CFR 312.32(c)(1)(i)(A)). For those adverse events that would not be reported unless an aggregate analysis indicated that they are occurring more frequently in the drug treatment group than in the placebo group, a determination that the adverse event is a suspected adverse reaction would require analysis and reporting of the event rates in both the drug-treatment and placebo groups.

To comply with the requirements for IND safety reports based on data in the aggregate, the sponsor should have in place a systematic approach for evaluating the accumulating safety data. A Data Monitoring Committee (DMC) or an independent sponsor safety team could perform this function (see sections V and V.A.3.c).

As described in section V.A.3.a, there should generally be no need to report unblinded study endpoints in an IND safety report. In many cases, an independent DMC would monitor the serious events that are study endpoints (see FDA's guidance document on *Establishment and Operation of Clinical Trial Data Monitoring Committees*).[10] If a sponsor has concerns that unblinding of adverse events will compromise the integrity of the study, the sponsor can propose in advance an alternative reporting format or frequency to maintain the blind that must be agreed to by the director of the review division in FDA with responsibility for review of the IND (21 CFR 312.32(c)(3)) (see section VI.A).

D. Investigator Reporting (21 CFR 312.64(b))

Most of the information about the safety of a drug prior to marketing comes from clinical trials. Therefore, adverse event reports from investigators are critically important, as they observe subjects' responses to the drug. Except for study endpoints, the investigator must immediately report to the sponsor all serious adverse events, regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure or in the investigator brochure as predicted to occur with the drug (21 CFR 312.64(b)). The Agency recognizes that it may take the investigator a short period of time (i.e., a day) to compile information about the event, but then expects the information to be immediately reported to the sponsor. Investigators are not required to determine whether an event is "unexpected," as defined in 312.32(a). This is a sponsor responsibility (see Appendix B).

Although it is the exception, immediate reporting of all serious adverse events to the sponsor may not be necessary in certain trials if the events are expected and well-defined. For example, many oncologic clinical trials use drugs with known serious hematologic adverse reactions and immediate reporting of each serious adverse event may not be useful. In these cases, the sponsor may propose an alternative reporting arrangement by identifying and describing the alternative reporting arrangement in the protocol or by requesting a waiver. The review division that has responsibility for the IND must agree to any alternative reporting arrangements (21 CFR 312.32(c)(3) and 312.10). Sponsor monitoring and reporting of these types of serious adverse events is discussed in section V.A.3.b.

[10] See footnote 4 for location.

1. Assessment of Causality

FDA believes that the sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the sponsor has access to serious adverse event reports from multiple study sites and multiple studies and is able to aggregate and analyze these reports (see section V.A). Moreover, the sponsor is more familiar with the drug's mechanism of action, class effects, and other information. For these reasons, investigators must immediately report any serious adverse event to the sponsor, whether or not the investigator considers the event to be drug related (21 CFR 312.64(b)).

In the report to the sponsor, the investigator must include an assessment of causality (i.e., whether there is a reasonable possibility that the drug caused the event) (21 CFR 312.64(b)). The investigator's view is important for the sponsor to consider when assessing the safety of the drug and determining whether to report an event expeditiously to FDA, because the investigator, who monitors the subject's response to the drug, is knowledgeable about the subject's clinical state (e.g., medical history, concomitant medications) and thus may be sensitive to distinctions between events that may be related to the drug versus those due to the underlying disease process and/or concomitant therapies. The sponsor should decide how to capture the investigator's causality assessment (e.g., rating scale, yes/no response to a question such as, "Was there a reasonable possibility that the drug caused the adverse event?").

2. Study Endpoints

The investigator must report study endpoints that are serious adverse events in accordance with the protocol (21 CFR 312.64(b)). Because endpoints are specifically defined in the protocol, they are often not collected on the adverse event pages of the case report form. The exception to this reporting requirement is when there is evidence suggesting a causal relationship between a drug and an event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the sponsor, even if the event is a component of the endpoint (e.g., all-cause mortality) (21 CFR 312.64(b)). "Safety endpoints" or "secondary endpoints," as described in section V.A.3.a, are not considered "study endpoints" and, therefore, must be reported to the sponsor immediately (21 CFR 312.64(b)).

3. Nonserious Adverse Events

The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol (21 CFR 312.64(b)). Generally, nonserious events are recorded on the case report forms and are submitted to the sponsor and reviewed at regular intervals during the course of the investigation. The

investigator's assessment of causality is not required for nonserious adverse events by the regulations, although many sponsors may require it in the protocol.[11]

For certain trials, such as a postmarketing outcome trial for a drug that has a well-established safety profile, it may be necessary for investigators to record only a subset of nonserious adverse events, or none at all. The sponsor can arrange that only specific types of adverse events be reported to the sponsor (e.g., those that resulted in withdrawal from the study or cessation of therapy, modification of dose, or addition of another drug) provided the director of the FDA review division that has responsibility for review of the IND has agreed to that arrangement in advance (21 CFR 312.32(c)(3)). Other nonserious adverse events would not need to be recorded by the investigator on the case report form.

E. Investigations of Marketed Drugs (21 CFR 312.32(c)(4))

According to 21 CFR 312.32(c)(4), a sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND must submit IND safety reports for suspected adverse reactions that are observed in the study, at either domestic or foreign sites. The sponsor must also submit safety information from the clinical study as prescribed by the relevant postmarketing safety reporting requirements (e.g., under 21 CFR 310.305, 314.80, 600.80, 606.170, or under the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109-462)). Note that § 312.32(c)(1)(ii) requires the sponsor to report findings from other studies that suggest a significant risk in humans, whether or not conducted under an IND and whether or not conducted by the sponsor. Therefore, as long as the sponsor maintains an open IND for a drug marketed or approved in the United States, safety information from foreign and domestic studies, including non-IND studies, must be reported to the IND and in accordance with the postmarketing requirements, if it meets the criteria for reporting.

For example, if an applicant of a drug marketed or approved in the United States sponsors a multicenter, multinational clinical trial for a new indication, where the domestic sites are included in an IND, adverse events from the clinical trial, whether or not the foreign sites are also conducted under the IND, must be promptly evaluated and reported if they qualify for reporting under § 312.32 and the postmarketing requirements.

If the same applicant or sponsor receives a spontaneous report of an adverse event from U.S. or foreign commercial marketing experience for a drug that is also under investigation, the report would not need to be reported to the IND because it is not a suspected adverse reaction observed in a study, but would need to be reported in accordance with the postmarketing reporting requirements, if it meets the criteria for reporting.

[11] CIOMS VI recommends that collection of investigator's causality assessments are not needed for routine regulatory reporting, but "there may be circumstances when such assessments are useful and important, such as for non-serious adverse events of special interest" (CIOMS 2005, at 85).

F. Adverse Event Reporting to Institutional Review Boards (IRBs)

Investigators are required to promptly report "to the IRB … all unanticipated problems involving risk to human subjects or others," including adverse events that should be considered unanticipated problems (21 CFR 312.66). In 2009, FDA issued a guidance on *Adverse Event Reporting to IRBs – Improving Human Subject Protection* that makes recommendations on the types of adverse event information that should be reported to an IRB.[12] The term *unanticipated problem* used in the *Adverse Event Reporting to IRBs* guidance describes adverse events and other types of problems (i.e., adverse events are a subset of unanticipated problems) that investigators are required to report to IRBs.

Although the rule on IND safety reporting does not directly address safety reporting by investigators to IRBs, questions have arisen about its impact on adverse event reports to IRBs, particularly with respect to the specific adverse events considered to be "unanticipated problems" that must be reported to the IRB. In general, a report that meets the criteria for reporting in an IND safety report should also be considered an "unanticipated problem" and reported to the IRB by the investigator.

It is important to note that some events that would not meet the criteria for reporting in an IND safety report would be considered unanticipated problems involving risk to human subjects (e.g., informed consent or privacy issues, certain adverse events that could not be caused by the investigational drug, such as events that occur prior to test article administration as a result of a washout period or due to a screening procedure). As part of their clinical trial monitoring responsibility, sponsors generally require that investigators report such unanticipated problems to them. Sponsors should discuss any significant unanticipated problem with the applicable FDA review division, as the problem may affect trial conduct and subject monitoring.

G. Duration of Safety Reporting

The purpose of sending IND safety reports to investigators is to provide investigators with information they need to protect their patients participating in clinical trials. Once they are no longer enrolling or monitoring patients, this information is no longer necessary. Cutoff dates for sending IND safety reports to investigators may be described in the protocol. If no cutoff dates are specified, once a site has been officially closed out, the sponsor usually does not need to continue sending IND safety reports to that site, and an investigator does not need to receive or review them. If the sponsor continues to send IND safety reports to the investigator and the investigator does not wish to continue receiving them, the investigator should contact the sponsor and request that the sponsor stop sending them.

In unusual cases, safety information related to delayed toxicity may be reported after a site is officially closed out. For example, if a late toxicity is discovered that would affect subjects who received the investigational drug, the investigator should be notified so that patients could be followed up if necessary.

[12] See footnote 4 for location.

H. IND Annual Reports and Labeling

The IND safety reporting requirements did not make any changes to the requirements for IND annual reports (21 CFR 312.33). FDA recently adopted the guidance for industry *E2F Development Safety Update Report*,[13] which describes a common standard for periodic reporting on drugs under development among the ICH regions and is intended to meet the IND annual reporting requirements. Questions have arisen about whether the Agency will accept the Development Safety Update Report (DSUR) because of the difference in the party responsible for making the causality judgment (see section III.C of this document). To promote global harmonization, FDA will accept the DSUR, as described in the *E2F Development Safety Update Report* guidance, to meet the IND annual report requirements.

The Agency does not expect the IND safety reporting requirements to have any impact on the adverse reaction information presented in prescription drug labeling.[14]

VII. SUBMITTING AN IND SAFETY REPORT (21 CFR 312.32(c)(1)(v))

A. Report Identification and Format

Each report must prominently identify its contents (21 CFR 312.32(c)(1)(v)).

- "IND safety report" for 15-day reports
- "Followup IND safety report" for followup information
- "7-day IND safety report" for unexpected fatal or life threatening adverse reaction reports

The type of report should be checked in box G7 on the FDA Form 3500A. The report can also be identified in box B5 and/or on a cover letter submitted with the FDA Form 3500A.

The format for IND safety reports is based on the type of expedited report.

1. Individual Cases

For reports of individual cases, a sponsor would ordinarily use FDA Form 3500A.[15] FDA will accept foreign suspected adverse reaction reports on a CIOMS I Form instead of FDA Form 3500A (21 CFR 312.32(c)(1)(v)). These forms should be completed with all available information, including a brief narrative describing the suspected adverse reaction and any other relevant information. If applicable, the narrative must also include identification of similar reports and an analysis of the significance of the suspected adverse reaction (21 CFR 312.32(c)(1)).

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[13] See footnote 4 for location.

[14] For more information, see 21 CFR 201.57(c)(7), 201.80(g) and the guidance for industry on *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. See footnote 4 for location.

[15] FDA Form 3500A can be found on the Internet at http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

2. Aggregate Reports

An IND safety report based on data in the aggregate must be in a narrative format (§ 312.32(c)(1)(v)). Sponsors should use judgment in deciding what to include in the narrative report. The report should include a description of the suspected adverse reaction, along with all relevant information, such as summary information about symptoms, concomitant medications, demographics, comorbid conditions, past history, pertinent laboratory test results, timing of events (onset and duration), and duration of treatment. Data from previously submitted individual case IND safety reports should be included, if applicable. Finally, the narrative report should describe the characteristics and results of the analysis, including a description of the databases, how the conclusion was reached, who reviewed the analysis, any planned changes in monitoring or to study documents (e.g., informed consent, investigator brochure), and any planned further analyses.

To evaluate the aggregated data in narrative format, FDA and participating investigators need the information on the individual cases that are summarized in the report. Therefore, at the same time that the narrative format IND safety report is submitted, the individual cases that were analyzed should also be submitted (e.g., a completed FDA Form 3500A for each case). If some individual cases were previously submitted as IND safety reports, they should be resubmitted and clearly identified as duplicates. Before submission, each individual case report should generally be unblinded. If a sponsor has concerns that unblinding will compromise the integrity of the study, the sponsor should discuss this in advance with the review division (see section VI.C).

If a sponsor is monitoring and evaluating the occurrence of a serious event in the aggregate (rather than submitting each case individually), FDA expects that records of each case will be complete (e.g., a completed FDA Form 3500A for each case), including a description of the suspected adverse reaction and any other relevant information, and that each case will be followed up for additional information, if necessary.

The sponsor should determine an appropriate approach for reporting subsequent occurrences of the same event to FDA and all participating investigators, and the sponsor should include a description of this approach in the initial expedited narrative IND safety report. For example, each subsequent occurrence of an infrequent event with immediate health implications or an event that is uncommon in a specific study population (e.g., stroke in young adults) should be reported in an expedited report. For an event that is known to occur independent of drug exposure in the study population, the sponsor may specifically describe an approach for reporting to FDA and all participating investigators (e.g., an updated aggregate narrative once a certain number of additional cases are identified or after a specified period of time, as appropriate).

3. Other Reports

For reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies, a narrative format must be used (21

CFR 312.32(c)(1)(v)). If the findings are published, in full or in abstract form, the sponsor should include a copy of the publication.

B. Where and How to Submit

The report must be transmitted to the CDER or CBER review division that has responsibility for review of the IND (21 CFR 312.32(c)(1)(v)). IND safety reports should be submitted to all of the sponsor's INDs under which the drug is being administered. For example, if a drug is found to cause drug induced liver injury, that should be reported to any IND under which the drug is being administered. The sponsor should reference all INDs to which the IND safety report is being submitted in the subject line of the cover letter. If applicable, the sponsor should also identify (e.g., with use of an underline) the specific IND under which the suspected adverse reaction occurred (e.g., "Suspected adverse reaction occurred under IND XXXX1, reference to INDs XXXX2, XXXX3"**)**.

FDA accepts electronic submission of 15-day IND safety reports in eCTD format to the IND application if the IND is in eCTD format or if the sponsor intends to convert the IND to eCTD format. Complete information on eCTD specifications and guidance can be found on the FDA eCTD Web site, and assistance may be obtained by contacting ESUB@fda.hhs.gov.

We recommend that sponsors submit 7-day IND safety reports electronically in eCTD format. If the IND is not in eCTD format, other means of rapid communication (e.g., telephone, facsimile transmission, email) may be used. If the IND is not in eCTD format and the sponsor intends to submit 7-day IND safety reports by facsimile transmission or email, the sponsor should address the submissions to the Regulatory Project Manager and the Chief, Project Management Staff in the FDA review division that has responsibility for review of the IND. In addition, if the sponsor intends to submit 7-day IND safety reports by email, we recommend the sponsor obtain a secure email account with FDA.[16]

C. Reporting Time Frame

The time frame for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting (21 CFR 312.32(c)(1)). The language in the IND safety reporting regulations was modified to describe the reporting time frame applicable to aggregate reports (§ 312.32(c)(1)(i)(B) and (C)) and increases in rates of occurrence of serious suspected adverse reactions (§ 312.32(c)(1)(iv)), which generally require more than one occurrence to make the determination that the event meets the criteria for reporting. Thus, the date of initial receipt of the first event could be well before it was determined that the event must be reported.

Sponsors should have a predefined safety monitoring plan that includes processes and procedures for the review of safety information, including the frequency of review (see section V). FDA

[16] Refer to the following link for details on obtaining a secure email account with FDA: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm.

expects that events that are interpretable as single cases (i.e., uncommon and known to be strongly associated with drug exposure) should be reported to FDA within 15 days from initial receipt. For events that require more than one occurrence to assess causality and events evaluated in the aggregate, the time clock starts when the sponsor determines that the events qualify for expedited reporting. This means that, for example, incomplete cases should be immediately followed up for additional information so that a determination can be made about whether the event is reportable as an IND safety report.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)). The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is no later than 7 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32(c)(2)). If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

The day of initial receipt for cases that are interpretable as single cases and the day the sponsor determines that multiple cases qualify for expedited reporting are considered day zero.

If FDA requests any additional data or information, the sponsor must submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request (21 CFR 312.32(c)(1)(v)). See section VIII for reporting time frames for followup information.

VIII. FOLLOWUP INFORMATION (21 CFR 312.32(d))

Most IND safety reports are derived from observations from clinical trials. In the setting of a clinical trial, information is collected in a controlled environment so that the information needed to evaluate the suspected adverse reaction (e.g., information that would be contained in a narrative report or on FDA Form 3500A) is generally readily available. If any information necessary to evaluate the suspected adverse reaction is missing or unknown, the sponsor should actively seek such information from the source of the report. Any relevant additional information that the sponsor obtains that pertains to a previously submitted IND safety report must be submitted as a *Followup IND Safety Report* without delay, as soon as the information is available (21 CFR 312.32(d)(2)), but should be submitted no later than 15 calendar days after the sponsor receives the information. The sponsor should maintain records of its efforts to obtain additional information.

For example, if information on concomitant medications is obtained after the initial IND safety report is submitted, and such information is relevant to evaluating the suspected adverse reaction, a sponsor must submit a *Followup IND Safety Report* immediately (21 CFR 312.32(d)(2)). However, if the sponsor obtains other information that is not relevant to evaluating the suspected adverse reaction, records of such information should be maintained by the sponsor and, if applicable, submitted in an information amendment (21 CFR 312.31) or in an IND annual report (21 CFR 312.33).

IX. SAFETY REPORTING REQUIREMENTS FOR BA AND BE STUDIES

The IND safety reporting requirements under 21 CFR 312.32 apply to BA and BE studies that are conducted under an IND. However, BA and BE studies that meet the conditions for exemption under 21 CFR 320.31 are not conducted under an IND and are not subject to the IND safety reporting requirements. The rule contains safety reporting requirements under 21 CFR 320.31(d)(3) that apply to persons conducting BA or BE studies that are exempt from the IND requirements. The following information addresses these requirements.

FDA believes that BA and BE studies that meet the requirements for exemption are generally safe. The occurrence of a serious adverse event is very unusual because the number of subjects enrolled in such a study is small, subjects are usually healthy volunteers, and drug exposure is typically brief. However, FDA occasionally receives safety-related information associated with these types of studies, which could reflect either a problem with the drug product being evaluated or with the study design being used. For these reasons, the occurrence of any serious adverse event, whether or not it is considered drug related, is of interest. Timely review of this safety information is critical to ensuring the safety of study subjects.

A. BA/BE Study Safety Reporting Requirements (21 CFR 320.31(d)(3))

The person conducting a BA or BE study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event observed during conduct of the study, regardless of whether the event is considered drug related, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence (21 CFR 320.31(d)(3)). This includes, for example, serious adverse events listed in the reference listed product's approved labeling, the investigator brochure, and protocol. Serious adverse events, whether observed in the investigational drug group or in the approved drug group (e.g., reference listed drug), must be reported (21 CFR 320.31(d)(3)).

If any information necessary to evaluate the serious adverse event is missing or unknown, the person conducting the study should actively seek such information and maintain records of efforts made to obtain additional information. Any relevant additional information that is obtained that pertains to a previously submitted safety report must be submitted as a *Followup Bioavailability/Bioequivalence Safety Report* as soon as the information is available (21 CFR 320.31(d)(3)), but should be submitted no later than 15 calendar days after the sponsor receives the information. In addition, upon request from FDA, the person conducting the study must submit to FDA any additional data or information that FDA deems necessary as soon as possible, but in no case later than 15 calendar days after receiving the request (e.g., hospital record, autopsy report) (21 CFR 320.31(d)(3)).

If the adverse event is fatal or life-threatening, the person conducting the study must also notify the Clinical Safety Coordinator in CDER's Office of Generic Drugs as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence (21 CFR 320.31(d)(3)). We recommend that these notifications be made by telephone, email, or facsimile transmission.

B. BA/BE Studies Conducted at Non-U.S. Sites

Under 21 CFR 320.31(d)(3), persons conducting human BA and BE studies in the United States that are exempt from the IND requirements under part 312 must report any serious adverse events from the study to FDA and to all participating investigators. The requirements under 21 CFR 320.31(d)(3) do not apply to human BA and BE studies that are exempt from the IND requirements and conducted outside of the United States. However, as part of the information required to establish that the proposed drug product can be expected to have the same therapeutic effect as the reference listed product, adverse event information from foreign clinical studies must be included in the abbreviated new drug application (ANDA) submission (see 21 CFR 314.94(a)(7)).

C. How and Where to Submit a Report (21 CFR 320.31(d)(3))

Each report must be submitted on FDA Form 3500A (21 CFR 320.31(d)(3)). The form should be completed with all the available information, including a brief narrative describing the serious adverse event, an assessment of causality, and any other relevant information. If applicable, the narrative should also include identification of other similar reports and an analysis of the significance of the serious adverse event. A summary of the study protocol should be submitted with the report.

Each report must prominently identify its contents (21 CFR 320.31(d)(3)).

- "Bioavailability/Bioequivalence safety report" for 15-day reports
- "Followup Bioavailability/Bioequivalence safety report" for followup information
- "7-day Bioavailability/Bioequivalence safety report" for unexpected fatal or life threatening adverse reaction reports

The type of report should be checked in box G7 on FDA Form 3500A. The report can also be identified in box B5 and/or in a cover letter submitted with the FDA Form 3500A.

The drug product should be listed in box C1 of FDA Form 3500A, and if the serious adverse event occurs in a subject receiving the investigational drug product, the drug administered during the BA/BE study should be identified as investigational and the established name of the reference listed drug should be identified.

Fifteen-day reports should be sent by email to OGD-PremarketSafetyReports@fda.hhs.gov. Paper reports may be sent to the Clinical Safety Coordinator, Office of Generic Drugs, in the Center for Drug Evaluation and Research at FDA.[17]

We recommend that 7-day notifications be made by telephone, email, or facsimile transmission. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

[17] The address for the Office of Generic Drugs is available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119100.htm. The phone and fax numbers (for fatal or life-threatening adverse event reports) are also available at this site.

X. REFERENCES

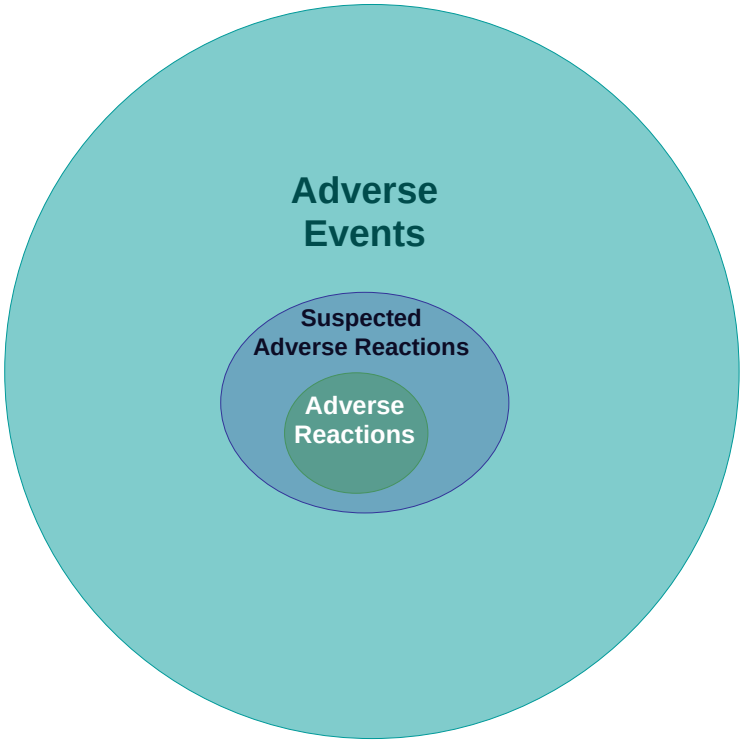
1. Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the Safety Planning, Evaluation and Reporting Team (SPERT). *Clin Trials* 2009: 6: 430-40.

2. Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI, 2005, *Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI*.

3. Xia HA, Crowe BJ, Schriver RC, et al. Planning and core analyses for periodic aggregate safety data reviews. *Clin Trials* 2011: 8: 175-182.

APPENDIX A: The Universe of Adverse Events

The diagram below depicts the relationship between adverse events, suspected adverse reactions, and adverse reactions.



APPENDIX B: Investigator and Sponsor Reporting Responsibilities

Reporting Responsibilities of Investigators under 21 CFR 312.64(b) and Sponsors under 21 CFR 312.32(c)(1)(i) for Serious and Unexpected Suspected Adverse Reactions

Term	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious (or life-threatening)	Yes (Investigator must report all serious adverse events to the sponsor immediately)	Yes	An event is considered serious or life-threatening, based on ***either*** the investigator's or sponsor's opinion.
Unexpected	No (No requirement to assess "expectedness")	Yes	The **sponsor** is responsible for determining whether event meets the definition of "unexpected," based on whether the event is listed in the investigator brochure; or if an investigator brochure is not required or available, is not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.
Suspected Adverse Reaction – (causality assessment standard - "reasonable possibility")	Yes (Investigator must provide sponsor with an assessment of causality)	Yes (Sponsor's assessment determines reportability, regardless of investigator's assessment)	The ***sponsor*** is responsible for determining whether there is a reasonable possibility that the drug caused the adverse event, taking into consideration the investigator's assessment.

↓

The *sponsor* reports serious and unexpected suspected adverse reaction to the FDA and all participating investigators.

Drug Treatment Studies – Placebo Use

Use of placebos in lieu of an approved FDA indicated drug may be appropriate where the investigator demonstrates that:

- standard therapy is unavailable or is of unproved efficacy, OR
- standard therapy possesses unacceptable side effects, OR
- minimal harm may result from the use of placebo (e.g., ongoing disease has little adverse effect on the patient during the course of the trial and is reversible), OR
- placebo itself may be an effective therapy, OR
- the disease process is characterized by exacerbation and remission.

If an investigator proposes a study in which a placebo is given for any length of time in lieu of an approved FDA indicated drug, the investigator must include risk management procedures in the research plan for the IRB for review.

The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself. The following issues should be specified:

- the frequency of monitoring,
- whether monitoring is in person or by telephone,
- the criteria for managing a subject in the event of worsening, and
- how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or withdrawal from the protocol.

IRB Determination

- The IRB may make its decision based upon the extent to which the above factors are demonstrated and upon a relative weighing of these and other factors.

- In discussing potential harm from the use of placebos, the investigators must provide a procedure for adequate monitoring of subjects to ensure their safety.

- To the extent that the investigator demonstrates that the subjects' safety is monitored at all times and provisions are made for immediate rescue if needed, the IRB will consider approval of the study.

- Once an approval is granted, the investigator is bound to follow the risk management procedures as with any other provision of the approved protocol.

Drug Treatment Studies – Washout Period

What is a Washout?

When a subject is asked to stop taking some or all medications prior to beginning a drug treatment study, this is called a drug washout.

Safety of Washout Studies

- Washouts are appropriate depending upon the disease to be studied and the nature of the proposed protocol.

- Washout studies require balancing the likelihood of harm, the effectiveness of monitoring, and the potential severity of the risk(s) to be avoided.

- When subjects are being washed out from a FDA approved and indicated drug, the individual investigator should clearly define the nature and degree of risk to the subjects and include risk management procedures in the research plan.

- The following issues should be clearly addressed by the investigator and determined to be appropriate by the IRB before the IRB should consider approval of the study:
  * when a subject would be withdrawn from the study,
  * the frequency of monitoring,
  * whether monitoring is in person or by telephone,
  * the criteria for managing a subject in the event of worsening, and
  * how 24 hour-per-day, 7 day-per-week, medical care is made available in the event of questions, emergencies, worsening, or withdrawal from the protocol.

- To the extent that the investigator demonstrates that the subjects' safety is monitored at all times and provisions are made for immediate rescue if needed, the IRB will consider approval of the study.

- Once an approval is granted, the investigator is bound to follow the risk management procedures as with any other provision of the approved protocol. The risk management procedures should be in the written protocol, with the same level of detail as in the protocol itself.

Emergency Use of a Test Article [Drug/Device]

The FDA human subjects regulations allow for an investigational drug/device to be used in emergency situations without prior IRB approval. Emergency use is defined as a life-threatening (severely debilitating) situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval for the use.

Criteria for Emergency Use

- No standard acceptable treatment is available
- No time to obtain prospective IRB approval
- An IND/IDE has been obtained for use of the investigational test article

NOTE: *FDA expects that this is a one-time occurrence at an institution for this particular test article. A second use in the same or different person normally requires prospective review.*

Requirements of the Investigator to the IRB

- Investigator must notify the IRB prior to use, if possible –
  * Per UI IRB SOP, this is a notification to an IRB-01 chair.
  * This is NOT considered IRB approval.

- Investigator is required to file a written report with the IRB within 5 working days indicating the clinical status of the patient, the protocol and consent used.

- Informed consent is required unless Investigator & a physician not otherwise participating in the clinical investigation certify in writing:

    1. The subject is confronted with a life-threatening situation necessitating the use of the test article.
    2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
    3. Time is not sufficient to obtain consent from the subject's legal representative.
    4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

Role of the IRB

- IRB chair may need to write a letter acknowledging notification if this is required by the sponsor in order to ship/use the test article.

- The investigator's report is presented by the IRB chair at the next available full board IRB meeting. When the IRB receives a report by an investigator of an emergency use, the IRB examines the case to assure that the emergency use was justified.

- If the IRB determines that the emergency use was not justified, this is considered noncompliance by the investigator.

HawkIRB Basic User Guide for IRB Members

To log on to HawkIRB
Go to the Human Subjects Office web site at www.research.uiowa.edu/hso and click on the "HawkIRB" icon in the upper left-hand corner of the screen. Log on with your hawkID and password.

To view a HawkIRB application
Type the IRB ID# of the study in the small textbox in the upper right-hand corner of the screen, and then click "Go." This takes you to the Project Summary screen for the study. You can return to this screen anytime while viewing the project by clicking "Go."

At the bottom of the screen under "History" you will see all of the applications that have been submitted for the project, in reverse chronological order.

- ***New Project applications***
  Click "New" under "History." The next screen shows the Form Review. Click each Roman numeral to go through the application section by section (if you "hover" the pointer of your mouse over the Roman numeral, the section title will pop up). To view the Consent Document and all other attachments, click the "Form Attachments" tab at the top of the screen, and then click on the name of each attachment.

- ***Modification applications***
  Click "Mod" under "History" (the "Mod" closest to the top of the list if there is more than one). Then click "Form Modifications" to view the changes being submitted and to see a side-by-side comparison of the old and new value. Attachments are listed at the bottom under "Attachments." If attachments have been changed, or new ones are being submitted, they will be listed on the right side of the screen with an asterisk (*). Click on the name of the attachment to view it. Changes will be tracked in a different font color.

- ***Continuing Review applications***
  Click "CR" under "History" (the "CR" closest to the top of the list if there is more than one). Click each Roman numeral (CRI, CRII, and CRIII) to go through the application section by section (if you "hover" the pointer of your mouse over the Roman numeral, the section title will pop up). To view the Consent Document and other attachments, go to the Project Summary screen (click "Go" in the upper right-hand corner), click the "Attachments" tab at the top of the screen, and then click on the name of each attachment.

- ***Continuing Review/Modification applications***
  Click "Mod/CR" under "History" (the "Mod/CR" closest to the top if there is more than one). Click each Roman numeral to go through the application section by section (if you "hover" the pointer of your mouse over the Roman numeral, the section title will pop up). Click "Form Modifications" to view the changes being submitted and to see a side-by-side comparison of the old and new value. Attachments are listed at the bottom under "Attachments." If attachments have been changed, or new ones are being submitted, they will be listed on the right side of the screen with an asterisk (*). Click on the name of the attachment to view it. Changes will be tracked in a different font color.

Legally Authorized Representative (LAR)

Children

In studies involving children in the state of Iowa, the legally authorized representative is:

- the parent, OR
- the court-appointed guardian.

A legal guardian in the state of Iowa is defined as a person who is not the parent of a child, but who has been appointed by a court or juvenile court having jurisdiction over the child, to have a permanent self-sustaining relationship with the child and to make important decisions which have a permanent effect on the life and development of that child and to promote the general welfare of that child. A guardian may be a court or a juvenile court.

Unless otherwise enlarged or circumscribed by a court or juvenile court having jurisdiction over the child or by operation of law, the rights and duties of a guardian with respect to a child shall be as follows:

a. To consent to marriage, enlistment in the armed forces of the United States, or medical, psychiatric, or surgical treatment.
b. To serve as a guardian ad litem, unless the interests of the guardian conflict with the interests of the child or unless another person has been appointed guardian ad litem.
c. To serve as custodian , unless another person has been appointed custodian.
d. To make periodic visitations if the guardian does not have physical possession or custody of the child.
e. To consent to adoption and to make any other decision that the parents could have made when the parent-child relationship existed.
f. To make other decisions involving protection, education, and care and control of the child.

Cognitively Impaired Adults

In studies conducted in the state of Iowa involving cognitively impaired adults, the legally authorized representative is:

- the designated proxy (such as a Durable Power of Attorney for Health Care)
- court-appointed guardian
- spouse [This does NOT include “common law” spouses]
- adult child
- parent
- adult sibling.

IMPORTANT NOTE: In studies involving cognitively impaired adults, permission must be sought from the first existing person in the above list, even if another relative is more conveniently available.

Motions – Full Board IRB

How to

- After discussion by the IRB, a motion is made from a board member.

- Examples of IRB motions new project, modification and continuing review applications include:
  - A motion was made to approve
  - A motion was made to approve pending required actions
  - A motion was made to table
  - A motion was made to disapprove

A motion to Approve

- Requires an assessment of the length of approval. The maximum approval is 365 days from the date of the meeting. The IRB can require a project to have review more frequently than annually – See the manual section called "CR – Criteria for More Frequent Review."

- Can only move to approve if no substantive changes required

- If IRB asks for new procedures for consent/recruitment materials a motion to approve can only occur if:

  - ✓ IRB determines specific wording
  - ✓ IRB only makes minor wording changes (typos, grammar)

  Then, if there are no other changes, motion can be to approve and minutes will indicate that IRB made these changes.

A motion to Approve Pending Required Revisions

- Requires an assessment of the length of approval. Unless the project qualifies for Biennial Review, the maximum approval is 365 days from the date of the meeting. The IRB can require a project to have review more frequently than annually – See the manual sections "CR – Criteria for More Frequent Review" And "CR – Biennial Review."

- By IRB approval pending required actions (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.

A motion to Table

- When the IRB requests of the PI/research team: clarification, additional materials, explanation, justification, simplification, amplification, provide additional… for ANY part of the application.

A motion to Disapprove

- Significant changes are needed
- Unethical to conduct the study

In the case of the review of Reportable Event Forms (REFs), since the form records an event and the IRB role is to review the event, there is no “approval/disapproval.”

Examples of IRB motions with regard to REFs include:

- A motion was made to accept the REF
- A motion was made to accept the REF pending required actions
- A motion was made to table the REF
- A motion was made to withdraw the REF

Voting – Full Board IRB

IRB members vote to agree or disagree with the motion or the member can choose to abstain (abstain is effectively counted as disagree).

At the discretion of the Chair, this vote may be by written ballot or a show of hands.

What constitutes approval of the motion?

- A majority count of “agrees” of the members present at the meeting is required for the motion to be approved.

What is recorded in the minutes regarding the motion & vote

- The official meeting minutes record the motion that was made from the board and the ***number of votes which agree or disagree*** with the motion as well as the number ***abstaining***.

- In the event a member of the IRB is not present for the discussion and vote, the minutes record the identity of the individual who was not present and, if the member was recused, the reason for recusal.

Non-English Speakers and Informed Consent

The IRB realizes that investigators cannot always anticipate when they will encounter non-English speaking individuals who may be eligible for a study. If this situation occurs, it may not be possible to translate the informed consent document into a language the individual understands in a timely manner. However, as outlined in The Belmont Report, to exclude such individuals from participating in a research study solely because they are unable to read, speak or understand English may not be an ethical practice in all cases. Therefore, the IRB allows the use of a Short Form to obtain consent in specific instances, and for a limited number of subjects.

Guidance for Principal Investigators and Research Team Members. The IRB provides the following guidance for obtaining consent with a Short Form when the research team encounters a potentially eligible, non-English speaking individual that is interested in participating in a study.

Short Forms are available in several languages. If there is a need for a Short Form in a language not available here, the Principal Investigator is responsible for using the English version as a template to translate the Short Form into any additional needed languages. Therefore, IRB review and approval of the Short Form is not required.

1. Download a Short Form in the appropriate language from the HSO website.
2. Enlist a translator who is fluent in both English and the potential subject's language
    a. Bilingual adult family members and significant others may serve as a translator
    b. If the study involves complex procedures, ensure the translator has an understanding of the technical information in the consent document
3. Allow the translator to verbally present the information in the IRB-approved English version of the ICD to the potential subject in his/her language, translate any questions the individual may have for the investigator, and provide the potential subject with the investigator's responses
4. Provide the potential subject with time to read the Short Form
5. Ensure that an individual over 18 years of age, fluent in both English and the subject's language, is present to witness the entire consent process
    a. The translator may also serve as the witness
    b. The witness must be unaffiliated with the study and fluent in both languages. Therefore, if the translator is the PI or a member of the study team, s/he may not also serve as the witness
    c. Bilingual family members and significant others may serve as witnesses
6. If the potential subject indicates agreement to participate in the study, the consent documents are signed. The non-English speaking participant (or LAR) signs the translated Short Form; and attests that the information in the ICD was presented orally in a language understandable to him/her (or LAR) and s/he consents to participate in the study
    a. The non-English speaking participant (or LAR) signs the translated Short Form; and attests that the information in the ICD was presented orally in a language understandable to him/her (or LAR) and s/he consents to participate in the study
    b. The research team member signs the IRB-approved English version of the informed consent document
    c. The witness signs both the Short Form and the IRB-approved English version of the informed consent document. By signing the Short Form, the witness attests to the fact that s/he observed the consent process, the information was presented in a language understandable to the subject, and the subject had the opportunity to ask

questions. The English version of the consent document does not have a separate signature section for the witness, so s/he will sign and date below the Person Who Obtained Consent

d. The translator signs the Short Form and affirms that s/he is fluent in both languages and orally presented the information in the English version of the consent document and answered any questions. If the translator is also the witness, s/he signs both the witness and translator signature sections on the Short Form

7. Provide the subject with copies of the IRB-approved English version of the consent form and the Short Form. Store the original, signed forms in the research records. Per IRB policy, the best practice is to store the signed ICDs (including Short Forms) separate from the subject data
8. The Principal Investigator must provide the subject with a translated version of the complete IRB-approved ICD within 30 days of enrollment if the study requires multiple visits or the subject's participation will last more than 60 days
9. Informed consent is an ongoing process. Therefore, the research team must address issues related to the subject's ability to communicate throughout the duration of the study. The best practice is to have a person of the subject's choosing, who is fluent in both languages accompany the subject to subsequent visits. Alternately, the research team may arrange for a translator to be available at subsequent visits to ensure that subject has an opportunity to ask questions, understands the responses and receives relevant study information

Consent to Participate in a Research Study

Subject's Full Name: _____ IRB ID #: __ __ __ __ __ __ __ __ __ __

Principal Investigator's Name: _____ Phone Number: _____

A University of Iowa investigator is inviting you to participate in a research study.

Before you decide whether to participate in this research study, the investigator must tell you:

1. the purpose of the research study
2. the study procedures
3. how long your involvement in the research will last
4. any procedures that are experimental
5. any reasonably foreseeable risks, discomforts, and benefits of the research
6. any potentially beneficial alternative procedures or treatments
7. how the confidentiality of your data will be maintained

Where applicable, the investigator must also tell you about:

1. any available compensation or medical treatment if injury occurs
2. the possibility of unforeseeable risks
3. circumstances when the investigator may stop your participation
4. any added costs to you
5. what happens if you decide to stop participating
6. new findings that may affect your willingness to participate
7. how many people will be in the study

A description of this research study may be available at www.ClinicalTrials.gov, as required by U.S. law for some studies. This website will not include information that can identify you. At most, the website will include a summary of the research results. You can search this website at any time. The investigator will tell you if a description of this study is available on the website.

If this research study involves the access or creation of Protected Health Information (PHI), the investigator must give you a copy of the University of Iowa Health Care *Privacy Notice* in your chosen language. If you choose to be in this study, you will sign the University of Iowa Health Care *Receipt of Privacy Notice Form* before you begin participation in this study and before any PHI is accessed or created. The investigator will provide these forms to you if the study involves PHI.

If you agree to participate, the investigator must give you a copy of this signed document in your chosen language and a copy of the IRB-approved full Informed Consent Document for this study, which is a summary of the research written in English.

Any time you have questions about the research, you may contact the Principal Investigator at the phone number listed above.

If you have questions or concerns about your rights as a research participant or about what to do if you are injured from participating in the research, contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242, (319) 335-6564, or e-mail irb@uiowa.edu.

Your participation in this research is voluntary, and you will not be punished or lose benefits if you refuse to participate or decide to stop participating at any time.

Participant
Your signature below means that a translator described the research study, including the above information, to you orally, the investigator has answered your questions, and that you voluntarily agree to participate in the research study.

Participant Printed Name _____

Participant Signature _____ **Date** _____

Translator
I affirm that I am fluent in both English and the following language, _____, and have orally presented the information in the English consent document to the 'Participant' listed above and answered any questions.

Translator Printed Name _____

Translator Signature _____ **Date** _____

Witness
I observed the entire consent process and attest that the information in the English version of the consent document was presented to the 'Participant' listed above, in the following language, _____, any questions were answered and the 'Participant' appeared to understand the information.

Witness Printed Name _____

Witness Signature _____ **Date** _____

Legally Authorized Representative Name (only if applicable)
Your signature below means that you are the legally authorized representative for the 'Participant' named above; and that the research study, including the above information, has been described to you orally, your questions have been answered, and that you voluntarily give consent for his/her participation in this research study.

Printed Name _____

Signature _____ **Date** _____

Research involving Pregnant women or fetuses

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

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

(b) the risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

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

(d) if the research holds out:
(1) the prospect of direct benefit to the pregnant woman,
(2) the prospect of a direct benefit both to the pregnant woman and the fetus, or
(3) 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 ---

(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; and

(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; and

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

Research Involving Neonates

45 CFR 46.205(a)

Neonates of uncertain viability and **nonviable neonates** may be involved in research if all of the following conditions are met:

1) *where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates;*
2) *each individual providing consent (under b(2) or c(5) of this section) is fully informed regarding the reasonably forseeable 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 46.205(b)

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

1) *the IRB determines that:*
   i) the research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
   ii) the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research;
   AND
2) *the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with Subpart A, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.*

45 CFR 46.205(c)

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

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

45 CFR 46.205(d)

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

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; shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

45 CFR 46.206(b):

If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

Prisoners in Research

§46.306 Permitted research involving prisoners.
(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(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.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

When an IRB is reviewing a protocol in which a prisoner is a subject or a proposed subject, the IRB must make, in addition to other requirements under 45 CFR 46, subpart A, seven additional findings under 45 CFR 46.305(a) in order to approve such research. They are:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; **and**

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

Prisoners & Epidemiological Research Waiver

(June 20th, 2003) The Secretary of Health and Human Services (DHHS), pursuant to 45 CFR 46.101(i), has waived the applicability of certain provisions of subpart C of 45 CFR part 46 (Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) to specific types of epidemiological research involving prisoners as subjects.

This waiver, effective June 20, 2003, will allow DHHS to conduct or support certain important and necessary epidemiological research that would not otherwise be permitted under subpart C.

The Secretary of HHS has waived the applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain epidemiologic research conducted or supported by DHHS

(1) in which the sole purposes are:

> (i) to describe the prevalence or incidence of a disease by identifying all cases, or
>
> (ii) to study potential risk factor associations for a disease,

and

(2) where the institution responsible for the conduct of the research certifies to the Office for Human Research Protections, acting on behalf of the Secretary, that:

- the institutional review board (IRB) approved the research and fulfilled its duties under 45 CFR 46.305(a)(2)-(7) and
- determined and documented that the research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and
- prisoners are not a particular focus of the research

Privacy and Confidentiality

Federal regulations [45 CFR 46.111(a)(7) (DHHS) and 21 CFR 56.111(a)(7) (FDA)] require that the IRB only approve research where there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

The investigator must have sound plans to protect the subject's identity, must collect only the necessary identified information to conduct the study, and must have procedures in place to maintain the confidentiality of the research records.

Although related, the concepts of privacy and confidentiality are distinct from one another. Privacy concerns people; confidentiality concerns data.

Privacy

- Privacy is the freedom from unauthorized intrusion or the state of being let alone and able to keep certain personal information to oneself.

- The evaluation of privacy should involve consideration of how the investigator will access information from or about participants.

- By its nature, research may invade the privacy of individual subjects in that it may require the collection, use, or access to identifiable information that would otherwise not be shared with others. When this is required for the purposes of the research, the private information involved should be the minimum necessary to accomplish the goals of the research.

Confidentiality

- Confidentiality means the ethical or legal right that information is considered private and will be held secret unless consent is provided permitting disclosure.

- IRB members should be knowledgeable of strategies to maintain confidentiality of identifiable data, including controls on storage, handling, and sharing of data.

- Investigators should explain the mechanisms that have been devised, for example, the use of numbering or code systems or safely locked files in private offices. The investigator should describe who has access to the data and under what circumstances a code system may be broken.

Record of Informed Consent

UIHC POLICY:

A. For any research protocol occurring in a UI Healthcare facility and involving the following requirements:

- Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit.
    - EXCEPTIONS: If a study does not meet the above requirements of having an EPIC Research Study link in the Electronic Health Record (EHR), the Principal Investigator is responsible for recording subject information in the Low-Risk Research Database that has been established by the Institute for Clinical and Translational Science, and may be accessed at https://redcap.icts.uiowa.edu/redcap/surveys/?s=yjnt3X .
    - Observational studies (that don't require physical interaction with the subject), participating in a written survey, oral interview or requesting an individual to participate in a data repository would ***not*** require documentation in either the UIHC EHR or the Low-Risk Database.

Documentation must be made in the subject's UIHC electronic medical record (either directly entered or scanned) and must include:

1. The "EPIC Research Study Description" (formerly known as the Record of Consent) approved by the Biomedical Institutional Review Board (IRB-01) is entered into the electronic medical record in EPIC under the "Research Studies" link.

    a. When accessing a patient on a study, there are multiple avenues to find the study information for the patient. Below, the user is in the visit navigator and there is a tab for "Research Studies" (1). Selecting this scrolls them to the study list for the patient. See example below:

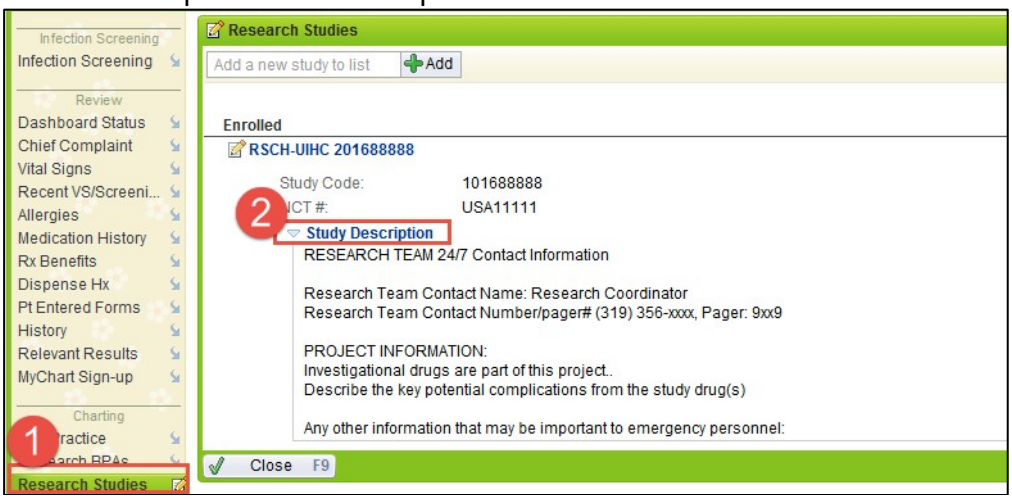


Figure 1. © 2017 Epic Systems Corporation. Used with permission.

2. Documentation to support billing, if appropriate.

B. For any use of an investigational medication, study medication, investigational device, or biologic occurring in a UI Healthcare facility, documentation must be made in the subject's UIHC electronic medical record and must include:

1. The "EPIC Research Study Description" language approved by the Biomedical Institutional Review Board (IRB-01)) is located in the research link which contains research study details relevant to clinical care.

2. Any applicable G-12 New Drug Data Form {entered or scanned into the electronic medical record}.

3. Documentation to support billing, if appropriate.

PROCEDURE:

Research/Study Protocols

A. If a research subject has any of the following occurring in a UI Healthcare Facility occur

- Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit

Documentation must be made in the subject's UIHC medical record. If the subject has a current UIHC medical record, the IRB approved content of the "EPIC Research Study Description" must be included in the EPIC Research Module found within the subject's UIHC electronic medical record. If the subject has no existing record, the subject must be registered as a UIHC patient and given a UIHC hospital number.

To create an EPIC Research Study, contact ICTS. ICTS uses the I-CART system to manage requests for various services to track progress and time spent on fulfillment. This guide will provide you with steps to submit a request via I-CART to create an EPIC Research Study.

https://wiki.uiowa.edu/display/ICTSit/How+to+request+a+service+in+I-CART

B. If services provided as part of the study will be billed to third party payors, appropriate documentation and required coding and billing regulations must be followed. Please refer questions to the Joint Office for Compliance Research Billing.

Research/Study Protocols Involving Investigational Medications or Study Medications

A. The investigator also must submit a completed G-12 New Drug Data Form to the Pharmacy and Therapeutics Subcommittee (form available from UIHC's medical record form site at http://forms.uihc.uiowa.edu/medicalrecordsforms.htm).

After receiving appropriate approvals, and obtaining the patient's consent, the Principal Investigator must ensure that the EPIC Research Study Description is complete and the G-12 Form are scanned into the patient's electronic medical record, as applicable.

B. For investigational medications that are obtained for individual patients as part of a treatment IND, single-patient use, emergency use, compassionate use, or similar protocol, the Principal Investigator must ensure the appropriate consent document and the G-12 Form are scanned into the patient's electronic medical record. The "Guide for Human Subject Research at the University of Iowa" (see section Emergency Use of an Investigational Drug or Device) provides additional information regarding Human Subjects Office requirements.

C. If services provided as part of the study will be billed to third party payors, appropriate documentation and required coding and billing regulations must be followed. Please refer questions to the Joint Office for Compliance Research Billing.

State Laws – Iowa Code

Iowa state law on the legal age to consent to treatments or procedures (see LAR section)

Iowa state law provisions on mandatory reporting:

1. Current abuse of a dependent adult (see Iowa Code Chapter 235 B):

"Dependent adult" is defined in §235B.2(4) as follows:
"Dependent adult" means a person eighteen years of age or older who is unable to protect the person's own interests or unable to adequately perform or obtain services necessary to meet essential human needs, as a result of a physical or mental condition which requires assistance from another, or as defined by departmental rule.

2. Current child abuse (see §232.69)
Note: §232.69(2) refers to permissive reporters ("any other person (i.e., other than listed in (1)) who believes that a child has been abused may make a report").

3. Other reporting
The general licensing provisions for a number of health care professions (see Iowa Code Chapter 147) require reporting a wound or "other serious bodily injury" that is being treated by the person licensed under that chapter and that appears to have been received in connection with the commission of a criminal offense.

Reportable conditions (see §641--1.1-1.3 (139A))

Additional state laws provide for the notification and surveillance of reportable communicable and infectious diseases, poisoning and conditions. Of note, in Iowa these include cancer and birth defects with reporting to the State Health Registry located at UI. When it is possible that identification of a reportable condition may occur in the research setting, investigators must include this information and the reporting requirements in the informed consent document.

Intent to hurt self or others

Common law (not statute) generally requires that one report a demonstration of a current intent to hurt oneself or others.

Iowa state law on Human Stem Cell Research and Cloning (Iowa Code 707C)

A person shall not intentionally or knowingly do any of the following:

- Perform or attempt to perform human reproductive cloning.
- Participate in performing or in an attempt to perform human reproductive cloning.
- Transfer or receive, in whole or in part, for the purpose of shipping, receiving, or importing, the product of human reproductive cloning.

Applicability of the laws of other states

In cases of human subjects research under the authority of the UI IRB(s) but conducted outside of the state of Iowa, the UI IRB confers with the UI Office of General Counsel regarding the applicability of other state, national, or international laws to the particular project. These cases are identified in the pre-review process of an application to the IRB and the advice of counsel is sought prior to the approval of the study. In general, the UI IRB will apply the law of the state in which the research is being conducted. For example, if a project involves children and one of the recruitment sites is in a bordering state, the laws of the bordering state will be evaluated to which individuals meet the DHHS and FDA definition of “children” at that site.

Partial Waiver of HIPAA Authorization

A waiver of HIPAA authorization is a regulatory determination that is made by the board. Under 45 CFR 164.512(i)(1)(i), an IRB of a covered entity can waive in full or in part the individual authorization required by HIPAA for use and disclosure of protected health information for research purposes.

In order for a research study to qualify for a waiver, the board must document that the use and disclosure of protected health information involves no more than minimal risk to the privacy of individuals based on evidence that the study has:

- An adequate plan to protect identifiers from improper use and disclosure
- An adequate plan to destroy the identifiers at the earliest opportunity
- Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity

In order to grant a waiver, the board must also determine and document that:

- the research could not practicably be conducted without a waiver
- the research could not practicably be conducted without access to protected health information

The board or IRB Chair can determine that a study qualifies for a partial waiver or a full waiver. The IRB can grant a partial waiver to allow for limited information to be collected from the medical record. For example, a partial waiver must be granted in order to collect eligibility information about potential subjects from the medical record such as whether a person or persons have a specific disease. One situation in which the IRB might grant a full waiver is for a medical record review study that has a waiver of consent.

Waiver of Elements of Consent
{45 CFR 46.116(c)(d)}
{Not available under FDA regulations}

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

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(i) public benefit or service programs;
(ii) procedures for obtaining benefits or services under those programs;
(iii) possible changes in or alternatives to those programs or procedures; or
(iv) possible changes in methods or levels of payment for benefits or services under those programs;

AND

(2) The research could not practicably be carried out without the waiver or alteration.

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

(1) The research involves no more than minimal risk to the subjects;

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

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

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

Waiver of Documentation of Informed Consent
{45 CFR 46.117(c)}

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

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

OR

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB must determine if the investigator is required to provide subjects with a written statement regarding the research.

FDA difference

Unlike HHS, FDA does not provide that an IRB may waive the requirement for signed consent when the principal risk is a breach of confidentiality because FDA does not regulate studies which would fall into that category of research.

Both regulations allow for waiver of documentation of informed consent in instances of minimal risk.

§46.116(e) Waivers of Consent for Public Health

(e) ***Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials***—(1) *Waiver.* An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (e)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) *Alteration.* An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (e)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) *Requirements for waiver and alteration.* In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

(i) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(A) Public benefit or service programs;

(B) Procedures for obtaining benefits or services under those programs;

(C) Possible changes in or alternatives to those programs or procedures; or

(D) Possible changes in methods or levels of payment for benefits or services under those programs; and

(ii) The research could not practicably be carried out without the waiver or alteration.

§46.116(f) General Waiver or Alteration of Consent

(f) ***General waiver or alteration of consent***—(1) *Waiver.* An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (f)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) *Alteration.* An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (f)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) *Requirements for waiver and alteration.* In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

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

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

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

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

(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

§46.116(g) Screening, Recruiting, or Determining Eligibility

(g) ***Screening, recruiting, or determining eligibility.*** An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

(1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or

(2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

(h) *Posting of clinical trial consent form.* (1) For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

(2) If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (*e.g.* confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

(3) The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

(i) *Preemption.* The informed consent requirements in this policy are not intended to preempt any applicable Federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that require additional information to be disclosed in order for informed consent to be legally effective.

(j) *Emergency medical care.* Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, state, or local law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe).

Office for Human Research Protections (OHRP)

NOTE: THIS GUIDANCE SUPERSEDES OHRP'S JANUARY 15, 2007 GUIDANCE ENTITILED "GUIDANCE ON CONTINUING REVIEW."
Office for Human Research Protections
Department of Health and Human Services

Guidance on IRB Continuing Review of Research

This guidance represents the Office for Human Research Protections' (OHRP's) current thinking on this topic. OHRP guidance 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 the Department of Health and Human Services (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 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 guidance document applies to research involving human subjects that is conducted or supported by HHS. It provides guidance on the HHS regulations for the protection of human research subjects at 45 CFR part 46 related to institutional review board (IRB) continuing review of research. In particular, the guidance addresses the following topics:

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:

The HHS regulations for the protection of human subjects at 45 CFR part 46 have several provisions pertinent to continuing review of research, including the following:

- An institution (or when appropriate an IRB) must prepare and maintain – and the IRB must follow – written procedures for:
    - Conducting continuing review of research and for reporting its findings and actions to the investigator and the institution;
    - Determining which projects require review more often than annually;
    - Determining which projects need verification from sources other than the investigators that no material changes in the research have occurred since the previous IRB review; and
    - Ensuring prompt reporting to the IRB of proposed changes in a research activity and for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the human subjects (45 CFR 46.103(b)(4), 46.108(a), and 46.115(a)(6)).
- No IRB may have a member participate in the IRB's continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e)).
- Except when an expedited review procedure is used, continuing review of research must occur at convened meetings at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas. In order for research undergoing continuing review to be approved, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)).

- *IRB approval* means 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 (45 CFR 46.102(h)).

- An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)).

- An IRB may use an expedited review procedure to conduct continuing review of research for some or all of the research appearing on the list of research eligible for expedited review (see http://www.hhs.gov/ohrp/policy/expedited98.html) and found by the reviewer(s) to involve no more than minimal risk. 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 IRB 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. For any research approved under an expedited review procedure at the time of continuing review, all members must be advised of such approvals. OHRP may restrict, suspend, terminate, or choose not to authorize an IRB's use of the expedited review procedure (45 CFR 46.110).

- In order to approve research, the IRB must determine that all of the requirements of 45 CFR 46.111 are satisfied. In addition, for research involving pregnant women, fetuses or neonates; prisoners; or children, the IRB must determine that the research satisfies the requirements of subpart B, C, or D, respectively, of 45 CFR part 46.

- An institution, or when appropriate an IRB, must prepare and maintain adequate documentation of IRB activities, including the following:

    - Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects;

    - Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of any controverted issues and their resolution;

    - Records of continuing review activities;

    - Copies of all correspondence between the IRB and the investigators;

    - Written procedures for the IRB in the same detail as required in 45 CFR 46.103(b)(4) and (5); and

    - Statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5) (45 CFR 46.115(a)).

Guidance:

A. Introduction

This guidance is intended to assist IRBs in carrying out their continuing review responsibilities under 45 CFR part 46 by providing recommendations regarding, among other things, the approval criteria, process, and frequency for continuing review to assure the protection of the rights and welfare of human subjects participating in research. The guidance also is intended to help investigators and others involved in the review, conduct, or oversight of research better understand their responsibilities related to continuing review.

An institution (or when appropriate an IRB) must prepare and maintain written procedures for conducting continuing review (45 CFR 46.103(b)(4)). The purpose of these written procedures is to ensure that IRBs have a framework for periodically reviewing the conduct of research by investigators. While a research project is ongoing, the IRB reviews and considers proposed changes to the research as they are received, including protocol and consent form

amendments. They also periodically receive and review reports of unanticipated problems involving risks to subjects or others (hereinafter referred to as "unanticipated problems") and other information about the research. In general, IRB review of a proposed change to a research project or a report of unanticipated problems during the period for which approval is authorized does not constitute continuing review of the project as a whole. Although an IRB may become familiar with various individual aspects of the research project's conduct, such familiarity does not relieve the IRB of the responsibility to conduct continuing review at least annually, which provides an opportunity to reassess the totality of the project and assure that, among other things, risks to subjects are being minimized and are still reasonable in relation to anticipated benefits, if any, to the subjects and the knowledge that is expected to result.

B. Key IRB Considerations When Evaluating Research Undergoing Continuing Review

1. Criteria for IRB Approval of Research Undergoing Continuing Review

HHS regulations set forth the criteria for IRB approval of research (45 CFR 46.111, 46.204-207, 46.305, and 46.404-409). These criteria apply to both initial review and continuing review of research and provide the framework for the IRB's evaluation of research. In order to re-approve research at the time of continuing review, the IRB must determine that all of following requirements are satisfied:

- 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 (45 CFR 46.111(a)(1));
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2));
- Selection of subjects is equitable (45 CFR 46.111(a)(3));
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 and 46.117, respectively (45 CFR 46.111(a)(4) and (5));
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6));
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (45 CFR 46.111(a)(7));
- Appropriate safeguards are included to protect subjects likely to be vulnerable to coercion or undue influence (45 CFR 46.111(b)); and
- When the research involves pregnant women, fetuses, or neonates; prisoners; or children, the research satisfies the additional requirements for IRB approval under HHS regulations at subpart B, C, or D, respectively, of 45 CFR part 46.

When conducting continuing review, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the above criteria. The IRB should focus on whether there is any new information provided by the investigator , or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document. IRBs have the authority to disapprove or require modifications in (to secure re-approval of) a research activity that does not meet the above criteria (45 CFR 46.109(a)). If research does not satisfy all of the above criteria, the IRB must require changes that would result in research satisfying these criteria, defer taking action, or disapprove the research.

When conducting continuing review and evaluating whether research continues to satisfy the

criteria for IRB approval of research, IRBs should pay particular attention to the following four aspects of the research:

- Risk assessment and monitoring;
- Adequacy of the process for obtaining informed consent;
- Investigator and institutional issues; and
- Research progress.

2. Risk Assessment and Monitoring

One of the most important considerations for the IRB at the time of continuing review is whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's previous conclusion that (1) the risks to subjects are minimized, and (2) the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(1) and (2)). The IRB's continuing review procedures should ensure that the IRB will consider relevant information received since the date of the last IRB review and approval of the research project from the investigator, any monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, a data and safety monitoring board (DSMB), or a data monitoring committee (DMC)), or any other source. Information regarding any unanticipated problems that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review regarding the risk:benefit relationship of the research (see OHRP's *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* at http://www.hhs.gov/ohrp/policy/advevntguid.html).

It also may be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring the research data to ensure safety of subjects (45 CFR 46.111(a)(6)) have been implemented and are working as intended (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

3. Evaluating the Adequacy of the Informed Consent Process

At the time of continuing review, the IRB should review a copy of the sample informed consent document submitted by the investigator to verify that the investigator is using the most recently approved version and that the document contains the most accurate, up-to-date information about the research. OHRP recommends that IRBs consider using methods that will allow the IRB to readily recognize the most current version of the IRB-approved informed consent document, for example, using date stamps, version numbers, or initialing and dating documents to indicate when a version was approved.

Likewise, if the IRB waived the requirement for the investigator to obtain a signed consent form for some or all subjects (45 CFR 46.117(c)), the IRB should assess the accuracy of the content of the information being provided to subjects orally and of any written statement regarding the research that is being provided to subjects.

When reviewing an informed consent document, the IRB must ensure that the currently approved or proposed consent document adequately addresses the elements of informed consent required under 45 CFR 46.116(a) and (b). The IRB should be particularly attentive to whether the informed consent document provides an accurate and up-to-date description of the reasonably foreseeable risks and discomforts of the research to the subjects (45 CFR 46.116(a)(2)) and any appropriate alternative procedures or courses of treatment that might be advantageous to the subject (45 CFR 46.116(a)(4)).

The IRB also should assess whether there is any new information presented by the investigator or others (for example, subjects or other individuals who have observed the investigator obtaining subjects' informed consent) that raises concerns about the circumstances under which informed consent is being obtained. For example, the IRB should assess whether there is any new information indicating that the investigator may not be

obtaining informed consent under circumstances that provide subjects with sufficient opportunity to consider whether or not to participate or that minimize the possibility of coercion or undue influence (see 45 CFR 46.116).

As part of the process for obtaining informed consent, subjects must be provided, when appropriate, with a statement that significant new findings developed during the course of the research which may relate to the subjects' willingness to continue participation will be provided to the subjects (45 CFR 46.116(b)(5)). Continuing review provides the IRB with an opportunity to determine whether there is any new information that should be considered to represent such a significant new finding and therefore be communicated to subjects who have already enrolled in the research (e.g., important new toxicity information or new adverse event information related to the research interventions that is identified during analysis of the research data; or new information regarding alternative treatments that have become available and may be advantageous to the subjects).

4. Evaluating Investigator and Institutional Issues

When appropriate, the reviewing IRB should consider issues regarding the investigator and the institution(s) where the research is being conducted during its continuing review, such as the following:

- Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, change in medical license status, or increase in number of research studies conducted by the investigator);
- Evaluation, investigation, and resolution of any complaints related to the investigator's conduct of the research;
- Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and applicable regulations, State and local law, or standards of professional conduct or practice; and
- Reports from any third party observations of the research carried out under 45 CFR 46.109(e).

5. Evaluating Research Progress

This section discusses three considerations for when the IRB evaluates the progress of a research study.

Confirmation that Continuing Review Information is Consistent with the IRB-approved Protocol

The IRB should confirm that the information provided by the investigator at the time of continuing review is consistent with the research protocol previously approved by the IRB. If this information suggests that the investigator is not conducting the research in accordance with either the IRB-approved protocol or the requirements or determinations of the IRB, the IRB should either defer re-approving the research or re-approve the research for a limited period of time (e.g., one month) and seek an explanation from the investigator regarding the apparent discrepancies.

Total Subject Enrollment

As part of its initial review of a research project, the IRB typically will have approved a protocol that includes the expected total number of subjects to be enrolled by the investigator and the expected rate of enrollment. Evaluating information about the number of subjects enrolled in the research at the time of continuing review may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol. A marked difference between the actual and expected rates of enrollment may indicate a problem with the research project that requires further evaluation, including whether the research project is likely to provide sufficient data to answer the scientific question(s) being posed.

Subject Withdrawals

Subjects may discontinue their participation in research at any point for various reasons (e.g., serious adverse events, conflicts with the investigators, transportation problems, etc.).

The IRB's continuing review procedures in general should provide for review of:

- The number of subjects who discontinued their participation; and
- A summary of the reasons for the withdrawals, if known.

IRB review of this information may shed light on problems related to the conduct of the research. For example, a high rate of subject withdrawal secondary to serious adverse events may indicate that the risks of the research are greater than expected and may lead the IRB to conclude that the research should not be approved for continuation because the risks to subjects are not being minimized or are not reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(1) and (2)).

C. Process for Conducting Continuing Review

1. Key Procedural Requirements for Continuing Review Conducted by the IRB at Convened Meetings

Continuing review must take place at a convened meeting at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas, unless the research qualifies for review under an expedited review procedure (45 CFR 46.108(b)). In order for research undergoing continuing review to be approved by the IRB at a convened meeting, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)). Should the quorum fail during a meeting (e.g., loss of a majority through exclusion (i.e., recusal) of members with conflicting interests or early departures of members, or absence of a nonscientist member), the IRB may not take further actions or votes for research projects undergoing continuing review unless the quorum can be restored (45 CFR 46.108(b)).

The IRB must ensure that no member participates in the IRB's continuing review of any research project in which the member has a conflicting interest, except to provide information requested by the IRB (46 CFR 46.107(e)).

For each research project undergoing continuing review, the minutes of IRB meetings must be in sufficient detail to show actions taken by the IRB; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving the research; and a summary of the discussion of controverted issues and their resolution. (45 CFR 46.115(a)(2)). OHRP recommends that the recusal of IRB members because of a conflicting interest also be documented when recording votes on IRB actions. The following examples demonstrate one acceptable format for documenting in the minutes the votes on actions taken by the IRB on research projects undergoing continuing review:

- Total = 15; Vote: For-14, Opposed-0, Abstained-1.
- Total = 14 (1 member recused and did not vote); Vote: For-12, Opposed-2, Abstained-0.

2. Key Procedural Requirements for Continuing Review Conducted Under an Expedited Review Procedure

When continuing review of research is conducted under an expedited review procedure, the review must be conducted by the IRB chairperson or one or more experienced reviewers designated by the IRB chairperson from among the IRB members (45 CFR 46.110(b)). The IRB must have procedures in place to ensure that no IRB member participates in the expedited review of research in which the member has a conflicting interest, except to provide information requested by the chairperson or his/her designee(s) (46 CFR 46.107(e)). The IRB chairperson or IRB members designated by the chairperson only can approve or require modification in (to secure approval of) research, but may not disapprove research using the expedited procedures (45 CFR 46.110(b)). Disapproval of a research project at the time of continuing review can only occur after review by the IRB at a convened meeting, not by the

expedited review process. All IRB members must be advised of research that has been approved under an expedited review procedure (45 CFR 46.110(c)).

See section E below for additional guidance regarding when an expedited review procedure may be used to conduct continuing review.

3. Written Procedures for Conducting Continuing Review

An institution (or when appropriate an IRB) must prepare and maintain – and the IRB must follow – written procedures for the continuing review of research (45 CFR 46.103(b)(4), 46.108(a), and 46.115(a)(6)). OHRP recommends that written procedures for continuing review describe the following:

- The procedures for informing investigators about their responsibilities related to continuing review under the HHS regulations at 45 CFR part 46 and the IRB's own policies and procedures on continuing review requirements;
- The list of documents to be submitted by investigators at the time of continuing review, the time frame for submitting these documents to the IRB, and the procedure for requesting these documents from the investigator (see sections C.4 and G below for further guidance);
- The list of specific documents distributed or made available to primary reviewers (if applicable) and to all other IRB members (see sections C.4 and C.5 below for further guidance);
- Any primary reviewer system used (see section C.6 below for further guidance);
- Any process (e.g., an administrative review process by IRB staff or a subcommittee review procedure) that may be used to supplement the IRB's continuing review (see section C.7 below for further guidance);
- For research requiring continuing review at a convened meeting, the timing of document distribution prior to IRB meetings;
- The range of possible IRB actions taken on research projects undergoing continuing review (see section C.9 below for further guidance);
- How continuing review under an expedited review procedure is conducted and how expedited approval actions are communicated to all IRB members;
- The procedures for:
    - Communicating to investigators IRB actions regarding continuing review of research and any changes or clarifications required by the IRB as a condition of IRB approval; and
    - Reviewing and acting upon investigators' responses to the IRB's requests for changes or clarifications;
- Which institutional office(s) and official(s) are notified of IRB findings and actions regarding continuing review and how notification to each is accomplished;
- The procedures for how the IRB determines the effective date of IRB approval following initial review of a research study and communicates this effective date and the initial period of approval to the investigator (see section G below for guidance regarding how to determine the effective date of initial IRB approval);
- The procedures for how the IRB determines continuing review dates for a research study (including whether the IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals) and communicates the period of approval following continuing review to the investigator (see section G below for guidance regarding how to determine continuing review dates);

- A procedure for how the IRB determines which protocols require review more often than annually, including specific criteria used to make these determinations (e.g., an IRB may set a shorter approval period for high-risk protocols or protocols with a high risk:potential benefit ratio; see section F below for additional guidance on determining the frequency of continuing review); and

- A procedure for how the IRB determines which projects need verification from sources other than the investigators (e.g., an independent study audit) that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (a) randomly selected projects; (b) complex projects involving unusual levels or types of risk to subjects; (c) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations at 45 CFR part 46 or the requirements or determinations of the IRB; and (d) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

4. Submission of Documents to the IRB

Investigators are responsible for fulfilling requirements associated with continuing review in time for the IRB to carry out continuing review prior to the expiration date of the current IRB approval. In particular, investigators are responsible for submitting sufficient materials and information for the IRB to meet its regulatory obligations, and should follow the institutional policies and procedures for continuing IRB review of research that are required by 45 CFR 46.103(b)(4) and referenced in the institution's OHRP-approved Federalwide Assurance (FWA). OHRP recommends that institutions have written procedures for continuing review that require investigators to submit the following documents, as applicable, <u>if not already available to the IRB as part of the existing IRB records for the research</u>:

- A brief project summary (this could be included as part of a progress report described in the next bullet, provided as a separate document, or be addressed by referencing other documents made available to the IRB, including the informed consent document(s));

- A progress report that includes the following:

    - The number of subjects accrued (for multicenter research studies, the number of subjects accrued at the local institution and the number accrued study-wide, if available, should be provided);

    - A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review;

    - Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research (note that OHRP does not expect the IRB to perform an independent review of the relevant scientific literature related to a particular research project undergoing continuing review; this responsibility rests with the investigators and any monitoring entity for the research);

    - A summary of both any unanticipated problems and available information regarding adverse events (the amount of detail provided in such a summary will vary depending on the type of research being conducted; in many cases, such a summary could be a brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and investigator's brochure (if applicable); see OHRP's *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* at http://www.hhs.gov/ohrp/policy/advevntguid.html);

    - A summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known; and

- A summary of any complaints about the research from subjects or others since the last IRB review;

- The latest version of the IRB-approved protocol and sample informed consent document(s);
- Any proposed modifications to the informed consent document or protocol;
- For FDA-regulated research, the current Investigator's Brochure, if available, including any modifications; and
- Any other significant information related to subject risk, such as the most recent report from any DSMB or DMC monitoring the research, if available. Even when the DSMB or DMC has identified no problems during its review and simply recommended continuation of the research study as designed, it may be useful for the IRB to be informed of this recommendation.

In developing procedures for continuing review, the IRB might consider use of templates, checklists, or other tools to standardize the request for information or list of materials to be provided to the IRB by investigators at the time of continuing review.

5. Distribution and Availability of Documents for Review by IRB Members

An IRB that is conducting continuing review of research should be familiar with, and have access to, all IRB records related the research, including those associated with the initial review and approval and any other previous reviews, including ad hoc and scheduled continuing reviews and any reviews of amendments to the research or unanticipated problems. For continuing review of research at a convened meeting, IRB members should receive appropriate materials sufficiently in advance of the meeting to allow adequate time for review.

OHRP recommends that for continuing review of a research study not eligible for expedited review all IRB members receive and review copies of the progress report described in the preceding section and the current IRB-approved informed consent document or any newly proposed consent document. At least one member of the IRB (e.g., a primary reviewer; see next section) should have available, for review as needed, the complete IRB file, including the complete protocol, relevant IRB meeting minutes, and any additional documents submitted by the investigator with the continuing review progress report. The complete IRB file also should be made available upon request to any IRB member prior to the meeting at which the research is to be reviewed and should be accessible during the meeting to allow members to resolve any questions that may arise during the IRB's deliberations.

When conducting continuing review of research under an expedited review procedure, the IRB chairperson (or designated IRB member(s)) should receive and review copies of the progress report described in the preceding section, the current IRB-approved informed consent document, and any newly proposed consent document, and have available, for review as needed, all of the above-referenced documentation, including the complete IRB protocol file.

6. Primary Reviewers

IRBs may adopt a variety of procedures to reduce burdens and allow the IRB to efficiently accomplish its continuing review workload. One such commonly-adopted procedure is the use of primary reviewers for continuing review of research at convened IRB meetings. Typically, primary reviewers are members of the IRB with appropriate expertise designated to perform primary review of IRB records related to research undergoing continuing review, provide an oral or written summary to the other IRB members, and lead the discussion at the convened IRB meeting. The primary reviewer's summary might highlight any critical issues for consideration by the IRB, identify any key changes being proposed by the investigator, and include recommendations for action by the IRB. A typical primary reviewer's summary might note that no issues of concern have arisen since the prior IRB review, no changes are being proposed by the investigator, adverse events are of the type and frequency expected, the research appears to satisfy all criteria required for approval under 45 CFR 46.111 (and

subparts B, C, and D when applicable), and the primary reviewer recommends approval without any stipulated changes.

7. Involvement of IRB Staff in Preliminary Review

Appropriately trained IRB staff members, regardless of whether they are members of the IRB, may perform preliminary reviews of continuing review documents and complete IRB files in order to facilitate the continuing review of research by the IRB. As part of this preliminary review, IRB staff may perform the following functions, among others:

- Confirm that all documents required by the IRB have been submitted by the investigator;
- Assess whether the information and documents submitted by the investigator are consistent with the research protocol previously approved by the IRB;
- Confirm that the informed consent document submitted by the investigator matches the current IRB-approved informed consent document;
- Aid the IRB in identifying important issues and concerns that the IRB may wish to consider; and
- Provide technical assistance and guidance to the IRB at convened meetings and to the IRB chairperson (or designated IRB member(s)) during an expedited review process.

IRB staff members who are *not* IRB members may not be delegated responsibility for making the determinations that must be made by the IRB at the time of continuing review (see sections B, C.1 and C.2 above) and may not approve research on behalf of the IRB (45 CFR 46.109).

8. Procedures for Continuing Review Deliberations During IRB Meetings

Research studies undergoing continuing review by the IRB at convened meetings should be considered and discussed individually. Furthermore, OHRP recommends that the IRB act and vote on research studies individually. If an IRB adopts a procedure under which the IRB votes on groups of studies (sometimes called "block voting") undergoing continuing review, such a procedure must provide IRB members with the ability to vote "yes" on some studies, "no" on others, and abstain on others (45 CFR 46.108(b)).

As previously noted, no IRB member may participate in the review of research in which the member has a conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e)). Individual consideration of, and voting on actions related to, research projects during continuing review will help to ensure that members with a conflicting interest related to a particular study do not participate in the IRB's continuing review of that study, except to provide information requested by the IRB.

OHRP recommends that minutes of IRB meetings document by name any member who had a conflicting interest in a research study and therefore was excluded (i.e., recused) from participation in the IRB's continuing review of that study, except to provide any information requested by the IRB. OHRP further recommends that, except when requested by the IRB to be present to provide information, IRB members absent themselves from the meeting room when the IRB conducts continuing reviews of research in which they have a conflicting interest, and that such also be noted in the minutes of the IRB meeting.

When conducting continuing review of a research project, the IRB, at its discretion, may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available to the IRB. The input of such expert consultants may be provided through (a) submission of written reports to the IRB prior to the IRB meeting at which a research project for which consultation was sought is to be reviewed and/or (b) the attendance and participation (either in person or by telephone or videoconference) of the expert consultants in the deliberations at the IRB meeting. These individuals may not vote with the IRB (45 CFR 46.107(f)), and their attendance at an IRB meeting must be documented in the minutes of the IRB meeting if they attend the meeting

(45 CFR 46.115(a)(2)). OHRP recommends that the minutes of the meeting also document the role any expert consultant played in the IRB's review.

The amount of time the IRB spends on the continuing review of a particular research project at a convened meeting will vary depending on the nature and complexity of the research, the amount and type of new information presented to the IRB by the investigator, and whether the investigator is seeking approval of substantive changes to the research protocol or informed consent document. For many research projects, continuing review can be fairly straightforward, and the IRB should be able to complete its deliberations and approve the research within a brief period of time.

For example, consider the continuing review by the IRB of a randomized clinical trial for which the investigator reports the following:

- The research is proceeding in accordance with the IRB-approved protocol;
- The rate of subject enrollment is as expected;
- There have been no unanticipated problems;
- The rate and pattern of adverse events is as expected;
- No subjects have complained about the conduct of the research or withdrawn from the research;
- There is no new published or unpublished information that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits and risks to the subjects and the informed consent process; and
- No changes to the protocol or informed consent document are needed.

In the absence of any concern about the research being raised by the IRB member assigned to be the primary reviewer or by any other IRB member present at the IRB meeting, the IRB should be able to complete its continuing review deliberations for such a research project within a brief period of time. In this example, deliberations that included the following brief series of steps would be sufficient:

- The primary reviewer provides a brief synopsis of the research and a statement that:
    - No concerning issues have arisen since the prior IRB review and approval;
    - No changes to the project are being proposed by the investigator;
    - Adverse events in subjects have been of the type and frequency expected;
    - The research appears to continue to satisfy all criteria for approval under the regulations at 45 CFR 46.111 (and subparts B, C, and D, when applicable); and
    - The reviewer recommends approval without any conditions.
- The IRB chairperson calls for a motion on the project;
- The primary reviewer makes a motion to approve the research without conditions and another member seconds the motion;
- The IRB chairperson makes a request for discussion by the IRB members; and
- Following any discussion, the IRB chairperson calls for a vote on the motion to approve the project without conditions.

On the other hand, consider the continuing review of a randomized clinical trial for which the investigator reports the following:

- The rate of serious adverse events occurring in subjects is significantly higher than expected;

- A recently completed research project reported in the literature identified previously unrecognized risks for the same experimental intervention being tested in the clinical investigator undergoing continuing review;

- The investigator is proposing several substantive revisions to the protocol in response to the new risk information, including the addition of new exclusion criteria and new safety monitoring procedures for subjects; and

- The investigator is proposing substantive changes to the informed consent document to add a description of the new information regarding reasonably foreseeable risks.

In these circumstances the IRB would need to spend significantly more time at the convened meeting on its continuing review of the research as it carefully reassesses whether the risks to subjects still are minimized and reasonable in relation to the to anticipated benefits, if any, to the subjects and the knowledge that is expected to result, given the new information presented by the investigator. The IRB also would need to assess whether the changes to the protocol and informed consent document proposed by the investigator are appropriate and adequate, or whether additional changes should be required.

9. Approving Research with Conditions at the Time of Continuing Review

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

- Approve the research study either (a) as submitted without any conditions, or (b) with conditions;

- Require modifications to secure approval and defer or table the research study for further review at a future date after the required modifications are submitted by the investigator (see section H for a discussion of how to handle lapses in IRB approval); or

- Disapprove the research study.

With respect to the first action listed above, by *IRB approval with conditions* (sometimes also referred to as "conditional approval" or "contingent approval") in the context of continuing review, OHRP means that at the time when the IRB reviews and re-approves a research study, the IRB as a condition of approval requires 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.

When approving research with conditions at the time of continuing review, 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. Note that OHRP would not consider such a suspension of subject enrollment at the time of continuing review to be a suspension of IRB approval that needs to be reported to appropriate

institutional officials, the head (or designee) of the agency conducting or supporting the research, or OHRP under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

For guidance regarding how to determine the effective date of initial IRB approval and the subsequent continuing review dates, see section G below. For additional guidance on IRB approval of research with conditions, see OHRP's *Guidance on IRB Approval of Research with Conditions* at http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html.

10. Additional Considerations Regarding Continuing Review Using an Expedited Review Procedure

When conducting continuing review under an expedited review procedure, the IRB chairperson or other member(s) designated by the chairperson, at their discretion, may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available to the IRB (45 CFR 46.107(f)). OHRP recommends that in such cases the IRB records document the involvement of such expert consultants in the expedited review.
However, only the IRB chairperson or experienced IRB members designated by the chairperson may carry out continuing review and approve research under the expedited review procedure.

An IRB administrator or staff member who is also an experienced member of the IRB may be designated by the IRB chairperson to conduct continuing review of research under an expedited review procedure.

OHRP also recommends that documentation for continuing reviews conducted under an expedited review procedure include:

- The specific categories permitting the expedited review; and
- Documentation of the review and action taken by the IRB Chairperson or designated reviewer.

See section E below for additional guidance regarding when an expedited review procedure may be used to conduct continuing review and recommendations regarding using an expedited review procedure to conduct continuing review when the only remaining human subjects research activities are limited to data analysis.

11. Using a Different IRB to Conduct Continuing Review

The IRB that conducted the initial review of a research project may be best suited to conduct continuing review of that project because of its familiarity with the research. However, an IRB other than the one that conducted the initial or other prior reviews of a research project may conduct continuing review of the project, as long as the IRB conducting the continuing review has members with appropriate experience and expertise and access to all prior relevant IRB records.

OHRP is aware that some institutions have designated one or more IRBs for the sole purpose of conducting continuing review. Such a practice is permissible under the HHS regulations for the protection of human subjects at 45 CFR part 46, as long as such IRBs satisfy the IRB membership requirements under 45 CFR 46.107 and fulfill the regulatory requirements for conducting continuing review referenced in this document.

D. Additional Considerations for Continuing Review of Multicenter Research Projects

When the HHS human subjects protection regulations at 45 CFR part 46 were first issued in 1974, the single investigator-single institution project was the norm, and reporting requirements to IRBs were almost entirely and appropriately fulfilled by the investigator, who was in a position to know about all aspects of the research project. Since that time, research projects involving multiple institutions (hereafter referred to as "multicenter research projects") have become commonplace. Although an individual investigator at a particular institution involved in a multicenter research project informs the local IRB at that institution about events related to subjects enrolled at that institution, the investigator and IRB are not likely to be well-informed about the progress of the research project across all institutions

involved in the research. Consequently, IRB review and oversight of such research has become more challenging.

1. Multiple Institutions Relying on Local IRBs for Continuing Review

For many multicenter research projects, most institutions involved in the research choose to rely upon an internal IRB operated by the institution (hereinafter referred to as a "local IRB") for both initial and continuing review of such projects.

As noted above in section C.4, OHRP recommends that institutions have written procedures for continuing review that require investigators to submit to the IRB at the time of continuing review a progress report that includes, among other things, summaries of any unanticipated problems, available information regarding adverse events, and any withdrawals of subjects or complaints about the research from subjects or others since the last IRB review. For continuing review of multicenter research at a particular institution, OHRP recommends that the local investigator include in the progress report a summary of such events for subjects who participated at that institution.

OHRP recognizes that local investigators participating in multicenter research projects usually are unable to prepare a meaningful summary of project-wide information, including information on adverse events, subject withdrawals, and complaints about the research, for their local IRBs because such project-wide information is not readily available to them. In such circumstances, when the research project is subject to oversight by a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC), OHRP recommends that at the time of continuing review local investigators submit to their local IRBs the most current report from the monitoring entity, if available. Such monitoring entities are in the unique position of having information for the entire project that may assist the IRBs in reviewing the research and protecting subjects. OHRP further recommends that such reports include the following:

- A statement indicating what information (e.g., project-wide adverse events, subject withdrawals, complaints about the research, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;
- The date of the review; and
- The monitoring entity's assessment of the information reviewed.

The local IRB has authority to require that such a report be submitted by the investigator and also may ask the monitoring entity directly to provide such a report (45 CFR 46.102(h) and 46.109(a)).

As discussed in section B.5 above, the IRB should evaluate information about the number of subjects enrolled in the research at the time of continuing review because a marked difference between the actual and expected rates of enrollment may indicate a problem with the project that requires further evaluation. When the local IRB at one institution is evaluating subject enrollment based on information provided by the local investigator, it may discover a much lower than expected rate of enrollment at that institution. In the absence of project-wide data being available to the IRB, such information may be indicative of lagging enrollment at that one local institution or at all institutions. In these circumstances, the local IRB should consider seeking additional information regarding project-wide enrollment. Project-wide enrollment data may indicate that there is sufficient rationale to continue the research project at the local institution despite low local enrollment because project-wide enrollment is progressing at the expected rate. Similar considerations would also apply to the local IRB's review of local subject withdrawals.

For any particular institution that chooses to rely upon a local IRB, continuing review of a multicenter research project by the local IRB at that institution must occur at least annually as long as the institution remains engaged in human subjects research activities involving the project (45 CFR 46.109(e)). Once the institution is no longer engaged in human subjects research activities under the project, there is no need for continuing review by the local IRB, even if human subjects research activities are occurring at other institutions. For example,

consider a multicenter clinical trial in which the following conditions exist with respect to institution A:

- The research is permanently closed to enrollment at the institution;
- All subjects enrolled at the institution have completed all-research related interventions and interactions, including interventions and interactions related to collection of long-term follow-up data;
- No additional identifiable private information about the subjects is being obtained by investigator at the institution; and
- The statistical center at another institution will conduct the analysis of all study data that includes identifiable private information about the subjects enrolled at institution A.

In these circumstances, the local IRB for institution A does not need to conduct any additional continuing review of the research project. This is the case even if the overall study results base has not been locked, such that there is the possibility that the statistical center at the other institution may query the investigators at institution A about previously collected data about the subjects enrolled at institution A. (Note that once the study results base for a study has been locked, no further changes can be made to the data set, and the only remaining activity is analysis of aggregate data.)

On the other hand, the local IRBs relied upon by other institutions where investigators continue to enroll subjects, intervene or interact with subjects, obtain identifiable private information about subjects, or analyze identifiable private information in accordance with the IRB-approved protocol would need to conduct continuing review of the research project at least annually.

2. Implementation of Cooperative IRB Review Arrangements for Continuing Review, Including Use of Central IRB Procedures

In the conduct of multicenter research projects, each institution engaged in the project is responsible for safeguarding the rights and welfare of human subjects and for complying with the requirements of 45 CFR part 46 (45 CFR 46.114). For multicenter research projects, an institution participating in the project may enter into a joint IRB review arrangement, rely on the review of a qualified IRB at another participating institution, or make similar cooperative IRB review arrangements for avoiding duplication of effort (45 CFR 46.114). These cooperative IRB review arrangements can be used for both initial and continuing review. OHRP encourages institutions engaged in multicenter research projects to utilize cooperative IRB review arrangements whenever it is appropriate and feasible to do so.

When an institution holding an OHRP-approved FWA relies upon an IRB operated by another institution or organization (i.e., an "external IRB") to review HHS-conducted or -supported research, the institution holding the FWA must execute an IRB Authorization Agreement (see http://www.hhs.gov/ohrp/assurances/forms/iprotsup.rtf) with the institution or organization operating the IRB (45 CFR 46.103(a) and 46.103(b)(2)); also see the Terms of the FWA at http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html#sectiona). Furthermore, when review responsibilities for a multicenter research project are shared across multiple IRBs under a cooperative review arrangement, OHRP recommends that the IRB Authorization Agreements or other written documents identify the responsibilities covered by the agreement and who is responsible for them.

It is important to note that each institution holding an OHRP-approved FWA has a responsibility to ensure that the IRBs upon which it relies collectively possess sufficient knowledge of the local research context for the research that they review on behalf of the institution.

Cooperative IRB review arrangements for a multicenter research project may vary with respect to how continuing review will be carried out. For example, all institutions engaged in a multicenter research project could designate the same IRB to conduct all aspects of continuing review on behalf of all institutions. Alternatively, all institutions engaged in a multicenter

research project could assign the same IRB the primary responsibility for continuing review of the research with respect to the assessment of project-wide information, but assign responsibility for assessment of local issues to each institution's local IRB. In both examples, the IRB that all institutions rely upon either partially or completely is commonly referred to as a "central IRB."

During its continuing review of a multicenter research project, a central IRB typically is responsible for reviewing a standard, project-wide protocol and the model/template informed consent document(s) that are distributed to investigators at all institutions engaged in the research. Depending on the nature of the cooperative IRB review arrangement, a central IRB at the time of continuing review also may be responsible for reviewing and approving the actual informed consent documents in use at one or more (or even all) institutions. If a central IRB conducting continuing review is responsible for the assessment of local issues, the central IRB should supplement its procedures as appropriate to ensure that local issues are addressed. For example, a central IRB should ask the local investigators or institutional officials for each institution relying on the central IRB to provide information related to subject withdrawals or complaints about the research. A central IRB's review of this information may shed light on problems related to the conduct of the research at a particular institution.

Whenever multiple institutions rely upon a central IRB to conduct continuing review of a multicenter research project that is overseen by a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC the project sponsor), OHRP recommends that the central IRB obtain a report describing project-wide information from that monitoring entity. Such monitoring entities are in the unique position of having information for the entire project that may assist the IRB in reviewing the research project and protecting subjects. The central IRB has authority to require that such a report be submitted by the investigators and also may ask the monitoring entity directly to provide such a report (45 CFR 46.102(h) and 46.109(a)). OHRP recommends that such reports include the same information as noted in section D.1 above.

E. When Expedited Review Procedures May Be Used by an IRB for Continuing Review

- **General Considerations**

IRBs may use an expedited review procedure to conduct continuing review of research projects that:

- Involve only procedures described in one or more of the nine categories of research activities published in the Federal Register (see 63 FR 60364-60367, November 9, 1998, also available at http://www.hhs.gov/ohrp/policy/expedited98.html); and
- Are found by the reviewers to involve no more than minimal risk to the subjects (45 CFR 46.110(b)).

Expedited review categories (1) to (7) apply to both initial and continuing review, whereas expedited review categories (8) and (9) apply only to continuing review.

In general, a research study that was eligible for initial review under an expedited review procedure will qualify for an expedited review procedure at the time of continuing review. However, IRBs should be aware that a research study previously approved under an expedited review procedure in some circumstances will need to undergo continuing review by the IRB at a convened meeting. For example, the investigator at the time of continuing review may propose changes to the research project that involve the addition of activities that do not fall within the scope of any of the categories of research activities eligible for an expedited review procedure.

Likewise, a research project that was *not* eligible for initial review under an expedited review procedure usually will *not* qualify for an expedited review procedure at the time of continuing review, except in the following limited circumstances:

- The research project involves only activities described by expedited review categories (8) or (9); or

- Research project previously approved by the IRB at a convened meeting progresses to the stage where all of the remaining human subjects research activities involve no more than minimal risk to the subjects and fall within the scope of one or more of expedited review categories (2) through (7).

2. Expedited Review Category (8)

Under category (8), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting as follows:

(a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **OR**
(b) Where no subjects have been enrolled and no additional risks have been identified; **OR**

- Where the remaining research activities are limited to data analysis.

For a multicenter research project, an expedited review procedure may be used by the IRB for a particular institution whenever the conditions of category (8)(a), (b), or (c) are satisfied for that institution. As a result, for some institutions involved in the conduct of a multicenter research project, the IRBs reviewing the project may need to conduct continuing review of the project at a convened meeting, whereas for other institutions, the IRBs may conduct continuing review using an expedited review procedure under category (8).

Expedited review category (8)(a) and the meaning of "long-term follow-up"

Under expedited review category (8)(a), OHRP interprets "long-term follow-up" to include:

- Research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys); and

- Collection of follow-up data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research protocol.

In contrast, OHRP interprets "long-term follow-up" to exclude:

- Research *interventions* that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.

However, some research studies that are not eligible for expedited review under category (8)(a) at the time of continuing review may be eligible for expedited review under one of the other expedited review categories. For example, if a research project's only remaining activity involves long-term follow-up of subjects by drawing 15 ml of blood once annually for a test that is not part of routine clinical practice, such research would not be eligible for expedited review under category (8)(a), but might be eligible for expedited review under category (2).

Expedited review category (8)(b)

With respect to category (8)(b), while the criterion that "no subjects have been enrolled" is interpreted by OHRP to mean that no subjects have ever been enrolled at a particular institution, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular institution has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.

Expedited review category (8)(c) and data analysis

OHRP considers a research study to continue to involve *human subjects* as long as the investigators conducting the research continue to obtain: (1) data about the subjects of the research through intervention or interaction with them; or (2) identifiable private information about the subjects of the research (45 CFR 46.102(f)). OHRP interprets *obtaining identifiable private information* to include an investigator's use, study, or analysis of identifiable private information. Therefore, as long as a non-exempt human subjects research study continues to

involve use, study, or analysis of identifiable private information by the investigators, the research continues to involve human subjects and must undergo continuing review by an IRB at least annually (45 CFR 46.109(e)), even if the participation of all subjects in a research project has been completed or discontinued. OHRP notes that simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subjects research and thus does not require continuing review.

Under expedited review category 8(c), an IRB may use an expedited review procedure to conduct continuing review when the only remaining human subjects research activity is the analysis of data that includes identifiable private information and the IRB chairperson (or another experienced IRB member designated by the chairperson) determines that this activity involves no more than minimal risk. OHRP expects that in nearly all cases such research activities will involve no more than minimal risk and therefore be eligible for IRB review under an expedited review procedure.

OHRP notes that the process for conducting continuing review of research under expedited review category (8)(c) can be accomplished through a simple, abbreviated process. For example, the investigator, as part of the continuing review process, could provide to the IRB the following statement regarding the research: "the study only involves data analysis, which is proceeding in accordance with the IRB-approved research protocol, and there are no problems to report." This statement could be provided by email or as part of a standard continuing review application form. Upon receipt of such a statement from the investigator, the IRB chairperson, or other member(s) designated by the chairperson, under the expedited review procedure may approve the continuation of the research project for another year without further deliberation or review.

For a multicenter research project, only the institution engaged in the ongoing data analysis activities (e.g., the institution operating the coordinating center or statistical center for the research project) needs to ensure that continuing review of the research by an IRB upon which the institution relies under its FWA occurs at least annually. Furthermore, when the data analysis activities progress to the point when they no longer involve analysis of identifiable private information (e.g., the overall study results base has been locked and the only remaining activity is analysis of aggregate data), further continuing review of the research is no longer required.

3. Expedited Review Category (9)

Under category (9), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified

With regard to the third condition, the IRB at a convened meeting must have determined that either (a) the research project as a whole involved no more than minimal risk, or (b) the remaining research activities involving human subjects present no more than minimal risk to the subjects. This determination, particularly with respect to (a), could occur as early as the convened IRB meeting at which the IRB conducted its initial review.

With regard to multicenter research projects, the fourth condition that "no additional risks have been identified" is interpreted by OHRP to mean that neither the investigator nor the IRB at a particular institution has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.

The following are two examples of research eligible for expedited review under category (9):

- A research study is designed to evaluate the effects of urban pollution on pulmonary status in healthy adults. The study is not conducted under an IND or IDE. The subjects are healthy adult volunteers living in urban settings who are asked to undergo monthly surveys regarding outdoor exercise activities and pulmonary symptoms, annual pulmonary function tests measured by routine spirometry procedures, and a single chest x-rays five years after enrollment. At the time of initial review, the IRB reviewed and approved the research at a convened meeting and determined and documented that the research involves no more than minimal risk. Because of the single chest x-ray five years after enrollment, the research at the time of initial review did not qualify for review under expedited review categories (1) through (7); in particular, category (4) explicitly excludes procedures involving x-rays. At the time of the first continuing review, the IRB chairperson (or another experienced reviewer designated by the IRB chairperson from among the IRB members) determines that the research continues to involve no more than minimal risk and that there have been no additional risks identified since the initial review. Therefore, the research study may undergo continuing review under expedited review under category (9).

- A research study is designed to evaluate the fluctuations in inflammatory cytokines in the serum of adult patients with newly diagnosed rheumatoid arthritis. The study is not conducted under an IND or IDE, and management of the subject's rheumatoid arthritis is determined clinically by the subject's primary rheumatologist and not by the investigator. The subjects are asked to undergo collection of 30 ml of blood by venipuncture 4 times per week for 6 weeks for measurement of serum inflammatory cytokines. The investigator plans to enroll 30 subjects per year for 3 years. At the time of initial review, the IRB reviewed and approved the research at a convened meeting and determined and documented that the research involves no more than minimal risk. Because of the frequency of blood collection, the research did not qualify at the time of initial review for review under expedited review categories (1) through (7); in particular, the frequency of blood draws exceeds that permitted under category (2). At the time of the first continuing review, the IRB chairperson (or another experienced reviewer designated by the IRB chairperson from among the IRB members) determines that the research continues to involve no more than minimal risk and that there have been no additional risks identified since the initial review. Therefore, the research may undergo continuing review under expedited review under category (9).

For additional guidance on the process for conducting continuing review of research eligible for review under an expedited review procedure, see section C above.

F. Determining the Frequency of Continuing Review

The IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less often than once a year (45 CFR 46.109(e)). In addition, the IRB must have and follow written procedures for conducting continuing review and for determining which projects require review more often than annually (45 CFR 46.103(b)(4) and 46.108(a)).

The IRB should decide the frequency of continuing review for each research project necessary to ensure the continued protection of the rights and welfare of research subjects. More frequent review (i.e., more frequently than once per year) may be appropriate, for example, when the risks to subjects warrants more frequent reassessment. OHRP recommends that the IRB consider factors such as the following when deciding on an appropriate interval for continuing review and that these factors be outlined in the IRB's written procedures for deciding the frequency of continuing review:

- The nature of any risks posed by the research project;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the investigators in conducting research;

- The IRB's previous experience with the investigators (e.g., compliance history, previous problems with the investigator obtaining informed consent, or prior complaints from subjects about the investigator);
- The projected rate of enrollment; and
- Whether the research project involve novel interventions.

At the time of initial approval of a research project, the IRB should specify the duration of the approval period and the interval by which continuing review must occur (e.g., 4 months, 6 months, or 1 year) in order for the research to continue. OHRP notes that in addition to specifying a time interval, the IRB also may specify a subject enrollment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the IRB might require that continuing review occur either in 6 months or after 5 subjects have been enrolled, whichever occurs first. OHRP also recommends that the minutes of IRB meetings clearly document the approval period (continuing review interval).

Similarly, OHRP recommends that at the time of continuing review the IRB consider whether the current frequency of continuing review for the research study is adequate or should be adjusted. For example, if the IRB initially approved a research study for a period of a year and at the first annual continuing review determined that the risks posed to the subjects have increased significantly, the IRB might re-approve the project after determining that the criteria for approval under 45 CFR 46.111 remain satisfied, but require that the next continuing review occur in 6 months.

The IRB's determinations regarding the approval of research and the required interval for continuing review must be communicated to the investigator in writing (45 CFR 46.103(b)(4) and 46.109(d)).

G. Determining the Effective Date of Initial IRB Approval and the Dates for Continuing Review

1. General Considerations

The IRB's written procedures should describe how the IRB (a) determines the effective date of IRB approval following initial review of a research study; (b) determines the continuing review dates for a research study; and (c) communicates these dates and the periods of approval to the investigator.

In general, IRB review of a proposed change to a research project during the period for which approval is authorized does not constitute continuing review of the project as a whole, and thus does not extend the date by which continuing review must occur (e.g., beyond one year from the effective date of the initial approval or the most recent continuing review approval).

Except when an expedited review procedure is used, the IRB must review proposed 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 (45 CFR 46.108(b)). In order for the research to be approved by the IRB at a convened meeting, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)). Therefore, for research not eligible for expedited review, approval by the IRB at the time of initial or continuing review must occur at a convened meeting of the IRB.

2. Determining the *First* Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting at the Time of Initial Review and Approved for One Year

*When the IRB Reviews and Approves Research **Without Conditions** at a Convened Meeting*

When an IRB conducts the initial review of a research project at a convened meeting and approves the research for one year *without* requiring either (a) changes to the protocol or informed consent document(s), or (b) submission of clarifications or additional documents, the effective date of the initial approval is the date of that IRB meeting. In such circumstances, the expiration date of the initial approval period and the date by which the **first** continuing review must occur may be as late as one year after the date of the IRB meeting at which the

research project initially was approved (45 CFR 46.109(e)). An example of this scenario is provided in the Appendix (see scenario A).

*When the IRB Reviews and Approves Research **With Conditions** at a Convened IRB Meeting Without Requiring Further Review at a Subsequent Convened Meeting*

A much more common scenario is when an IRB conducting the initial review of a research project at a convened meeting takes the following set of actions:

- Approves the project for one year;
- As a condition of approval, requires either (a) changes to the protocol or informed consent document(s), or (b) submission of confirmations of specific assumptions or understandings on the part of the IRB or additional documents; and
- Directs that the IRB chairperson (or other individual(s) designated by the IRB) to review and determine on behalf of the IRB whether the changes, clarifications, and/or additional documents to be submitted by the investigator(s) are satisfactory (see OHRP's *Guidance on IRB Approval of Research with Conditions* at http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html).

Under this scenario, further review by the IRB at a subsequent convened meeting is not necessary in order for the initial approval to become effective, and 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 all changes to the protocol or informed consent documents, or any other responsive materials, required by the IRB from the investigator. In such circumstances, the expiration date of the initial approval period, which is the date by which the first continuing review must occur, may be as late as one year after that effective date of initial IRB approval (45 CFR 46.109(e)). OHRP notes that the first continuing review in these circumstances may occur earlier; for example, for logistical reasons an IRB may choose to set the expiration date of the initial approval period at one year from the date of the IRB meeting at which the research project initially was approved with conditions. Examples of these scenarios are provided in the Appendix (see scenarios B1-B3).

The IRB records must include documentation of the date when the IRB chairperson (or other individual(s) designated by the IRB) determined that all conditions of IRB approval have been satisfied and the approval becomes effective, and the expiration date of the initial IRB approval (i.e., the date by which the first continuing review must occur) (45 CFR 46.102(h) and 46.115(a)).

In circumstances where an IRB at a convened meeting approves a research study with conditions, OHRP recommends the following:

- The IRB should consider implementing administrative procedures to minimize the time between the IRB's review and approval of the research study at the convened meeting and the investigator's submission of revised protocol or informed consent documents or any other responsive materials requested by the IRB (e.g., the IRB might require, if appropriate, that (a) the investigator submit such materials within 1, 3, or 6 months of the IRB meeting, and (b) if the investigator misses such a deadline, the research study be reviewed again by the IRB at another convened meeting upon receipt of the responsive materials from the investigator); and
- When responding after a prolonged period of time to the IRB's request for either (a) changes to the protocol or informed consent document(s), or (b) submission of clarifications or additional documents, the investigator should inform the IRB of any new information (e.g., new information about risks of the research interventions) the investigator has become aware of since the convened IRB meeting that might alter the IRB's determinations under 45 CFR 46.111 and, if applicable, subparts B, C, and D of 45 CFR part 46.

3. Determining the Date for the *Second and all Subsequent* Continuing Reviews for Research Reviewed by the IRB at Convened Meetings and Approved for One Year

Intervals, Including How to Maintain a Fixed Anniversary Date for the Expiration of Annual IRB Approvals

An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)). Given this requirement, it is important to recognize that the use of the "effective date" of IRB approval (i.e., the date on which the IRB chairperson or any other individual(s) designated by the IRB has determined that the conditions of approval have been satisfied) – as opposed to the date of the convened meeting at which the IRB approved a research study with conditions as described in the section G.2 above – to determine the latest permissible date for continuing review *only applies to the first continuing review*. For all subsequent continuing reviews of a research study, since there will be an on-going approved study, *the date of the convened meeting* when the IRB conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

OHRP notes that when the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse even if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB's conditions (see section C.9 above for additional guidance on approval of research with conditions at the time of continuing review and section H below for additional guidance on lapses in IRB approval).

OHRP recognizes the logistical advantages of keeping the expiration date of the IRB approval period constant from year to year throughout the life of a research project. Therefore, when (a) the IRB grants approval for one year at the time of each continuing review, and (b) the IRB performs continuing review and re-approves (with or without conditions) the research within 30 days *before* the IRB approval period expires, the IRB may retain the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period. For example, if an IRB conducts initial review of a research project and approves it without conditions on October 1, 2009 for one year, the IRB may conduct its first continuing review anytime between September 1 and October 1, 2010, and re-approve the research for another one-year period that expires on October 1, 2011. The same timing may be applied to each subsequent continuing review until the research activities involving human subjects are completed. Institutions that adopt a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals should include a description of this procedure in their written IRB procedures (see section C.3 above for additional guidance on written IRB procedures for conducting continuing review).

Determining the dates for continuing reviews after the first continuing review should be straightforward. The Appendix includes several scenarios that provide further clarification regarding how to implement this guidance in circumstances where the IRB approves research at the time of continuing review at a convened meeting either with or without conditions (see scenarios C1-C7).

4. Determining the Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting and Approved for Less Than One Year and for Research Reviewed by the IRB Under an Expedited Review Procedure

The same guidelines for determining the continuing review dates as discussed in sections G.2 and G.3 above would apply when the IRB determines that a research project must undergo continuing review more often than annually (see section F above) and when the IRB reviews and approves research under an expedited review procedure (45 CFR 46.110). Examples of both types of scenarios are provided in the Appendix (see scenarios D1-D3 for research reviewed more often than annually and scenarios E1-E2 for research reviewed under an expedited review procedure).

H. Lapses in IRB Approval

As previously noted, continuing review of research must occur at intervals appropriate to the degree of risk, but not less frequently than once per year (45 CFR 46.109(e)). OHRP recommends that the IRB establish written procedures for informing investigators of the HHS

regulations at 45 CFR part 46 and the IRB's own policies and procedures on continuing review requirements. This applies whether the research projects are reviewed by the IRB at a convened meeting or under an expedited review procedure.

OHRP recommends that the IRB and the investigator plan ahead to ensure that continuing review and re-approval of research occurs prior to the end of the approval period specified by the IRB. OHRP further recommends that the IRB's written procedures provide for sufficient advance notice to the investigator to ensure that the requirements for continuing review are met by the date on which approval would expire. The IRB should develop administrative procedures, such as computerized tracking systems, to minimize any unintended expiration of IRB approval. OHRP cautions, however, that if investigators submit materials for continuing review too far in advance of the expiration date of IRB approval, the materials may not reflect the current status of the research by the time that continuing review actually takes place. Therefore, OHRP recommends that the IRB work to link as closely in time as possible:

- The receipt by the IRB of continuing review materials;
- The review of those materials by the IRB; and
- The impending expiration date for IRB approval.

OHRP notes that it is the responsibility of investigators to provide in a timely manner the information needed by the IRB to perform its continuing review functions, and any reminder notices regarding the need to do so from the IRB to investigators are a courtesy.

The HHS regulations at 45 CFR part 46 make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research – with or without conditions – by the expiration date of IRB approval. In such circumstances, all research activities involving human subjects must stop after IRB approval expired, *unless* it is determined to be in the best interests of already enrolled subjects to continue participating in the research. Enrollment of new subjects cannot occur after the expiration of IRB approval. Continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects (see section J below for additional guidance).

The determination regarding whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired may be made initially by the investigator, possibly in consultation with the subjects' treating physicians (if the investigator is not the subjects' treating physician), but the investigator as soon as possible should submit a request for confirmation that the IRB agrees with this determination. The determination by the IRB may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. Furthermore, this determination may be made for all enrolled subjects as a group or for each individual subject. If the investigator or IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects (45 CFR 46.109(a) and (e)).

When IRB approval of an ongoing research project lapses and the investigator wants to continue the project, the IRB should complete continuing review for the project as soon as possible. Investigators may resume the human subjects research activity once continuing review and approval by the IRB has occurred. OHRP recommends that the IRB document why the lapse in IRB approval occurred, and, if appropriate, any corrective actions that the investigator, institution, or IRB is taking to prevent any such lapse of approval of the project from occurring again in the future.

Furthermore, when IRB approval of an ongoing research project lapses and the IRB subsequently re-approves the project, the IRB may approve the project for one year and

establish a new anniversary date for the expiration date of subsequent approval periods, or the IRB may re-approve the project for a period of less than 1 year so as to retain the original anniversary date on which prior approval periods expired (see scenario C7 in the Appendix).

When continuing review of a research project does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. OHRP does not consider such an expiration of IRB approval to be a suspension or termination of IRB approval. Therefore, such expirations of IRB approval do not need to be reported to OHRP as suspensions or terminations of IRB approval under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). However, if the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is frequently not meeting the continuing review dates), the IRB should determine whether such a pattern represents serious or continuing noncompliance that needs to be reported to appropriate institutional officials, the HHS agency that supported the research, and OHRP (45 CFR 46.103(b)(5).

I. Communicating the IRB's Continuing Review Determination to Investigators and the Institution

The IRB must notify the investigator and the institution in writing of its decision to approve or disapprove proposed research, or of modifications required to secure IRB approval of the research (45 CFR 46.103(b)(4) and 46.109(d)). Furthermore, if the IRB decides to disapprove research, it must include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing (45 CFR 46.109(d)). These notification requirements apply to both initial and continuing review. Therefore, after an IRB completes its continuing review of a research project, the IRB must provide written notification informing the investigator of the IRB's determination (e.g., approval, requiring modification(s) to secure approval, or disapproval). OHRP also recommends that the IRB notify any sponsor or coordinating center of a study (possibly through the investigator) of any decision to disapprove the research and the reasons for its disapproval determination.

For research projects that are approved to continue, the IRB's notification to the investigator must clearly state the period of time for which the project is approved, any conditions of the IRB's approval, and the date by which the next continuing review must occur (45 CFR 46.103(b)(4) and 46.109(d))(see section G above for additional guidance on how to determine the effective date of initial IRB approval and continuing review dates). OHRP also recommends that written IRB procedures related to continuing review describe which institutional office(s) and official(s) are notified of IRB findings and actions regarding continuing review and how notification to each is accomplished.

J. Suspension or Termination of IRB Approval of Research or Disapproval of Research at the Time of Continuing Review

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that is associated with unexpected serious harm to subjects (45 CFR 46.113). A suspension or termination of IRB approval of research may occur at anytime during the period for which IRB approval had already been given.

For a multicenter research project for which many or all institutions engaged in the research project choose to rely upon their local IRBs for review of the project, a local IRB's decision at one institution to suspend or terminate its approval of the research only applies to the conduct of the research project at that institution. On the other hand, if all institutions engaged in a multicenter research project rely upon a central IRB for review of the project, the central IRB could suspend or terminate its approval of the research either at one institution because of a unique problem regarding the conduct of the research at that institution or at all institutions because of a study-wide problem.

Suspension of IRB approval may be appropriate when a significant issue is first identified and while the IRB investigates the matter. For example, if there is an allegation of serious noncompliance by an investigator or a human subject safety issue that needs further

investigation and evaluation, the IRB may decide to suspend its approval of the research project while the allegation or issue is undergoing evaluation. In addition, the IRB may consider whether it is appropriate to notify subjects about the suspension and the reasons for it, and if so, when the subjects should be notified, given that complete information may not be available.

Any suspension or termination of IRB approval must be promptly reported to the investigator, appropriate institutional officials, the HHS agency that supported the research, and OHRP (45 CFR 46.103(b)(5) and 46.113)**.** Such reports must include the reasons for the IRB's action (45 CFR 46.113).

IRBs must follow written procedures for ensuring such reporting (45 CFR 46.108(a)). When reporting the suspension or termination of IRB approval of a research project to OHRP, OHRP recommends that the report include the following information:

- The name of the institution(s) (e.g., university, hospital, foundation, school, etc) conducting the research project;
- The title of the research project and the title of any related grant, contract, or cooperative agreement;
- The name of the principal investigator for the research project;
- The number of the research project assigned by the IRB and the number of the applicable HHS award(s) (grant, contract, or cooperative agreement);
- A detailed description of the reason for the suspension or termination; and
- The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.)

When an IRB (a) suspends or terminates its approval during the period for which IRB approval had already been given or (b) disapproves a research project at the time of continuing review, the IRB should establish procedures to ensure that the rights and welfare of currently enrolled subjects are protected, subjects are not put at risk, and subjects receive appropriate care, if indicated, during the period of suspension or following the cessation of the research. This is particularly important in the context of clinical trials. For example, the IRB, in consultation with the investigator and the subjects' treating physicians (if not the investigator), may need to determine whether it is in the best interests of currently enrolled subjects to (a) continue receiving the interventions that were being administered to subjects under the research project, (b) be transferred to another institution engaged in the research so that participation of the subjects in the research may continue, or (c) be transitioned to medical management outside of the research context. Continuation of subjects on interventions that were being administered under the research project may be appropriate at least temporarily, for example, when those interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

K. Identifying the Point When Continuing Review is no Longer Necessary

Continuing review and re-approval of a research project at least annually is required so long as the project continues to involve human subjects. OHRP considers a research project to continue to involve human subjects as long as the investigators conducting the research continue to obtain:

- Data about the subjects of the research through intervention or interaction with them; or
- Identifiable private information about the subjects of the research.

With respect to *obtaining identifiable private information*, OHRP considers this to include obtaining identifiable biological specimens originating from living individuals. *Furthermore, OHRP considers obtaining identifiable private information to include*:

- Collecting or receiving identifiable private information (including identifiable biological specimens) from any source (i.e., not already in the possession of the investigator);
- Collecting identifiable private information by observing or recording private behavior without interacting or intervening with the human subjects; and
- Using, studying, or analyzing identifiable private information (including identifiable biological specimens), even if the information was already in the possession of the investigator before the research begins. This includes using, studying, or analyzing any of the following:
    - Identifiable private information obtained by interacting or intervening with the human subjects;
    - Identifiable private information stored in documents, records, photographs, images, video recordings, or audio recordings provided to the investigators from any source;
    - Identifiable private information stored in documents, records, photographs, images, video recordings, or audio recordings already in the possession of the investigator before the research begins;
    - Identifiable private information obtained about an individual by interviewing other people (e.g., an individual's healthcare provider or teacher);
    - Identifiable biological specimens provided to the investigators from any source; or
    - Identifiable biological specimens already in the possession of the investigator before the research begins.

A research project no longer involves human subjects once the investigators have finished obtaining data through interaction or intervention with subjects or obtaining identifiable private information about the subjects, which includes the using, studying, or analyzing identifiable private information. Once all such activities described in the IRB-approved protocol are finished, the research project no longer needs to undergo continuing review. For example, when the only remaining activity of a research project involves the analysis of aggregate data sets without individual subject identifiers, no further continuing review is necessary. At that point the IRB can formally close the IRB file for that project and advise the investigator of that action.
Similarly, simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subjects research and thus does not require continuing review. See section D.1 above for additional guidance on determining when continuing review is no longer required for a particular institution involved in the conduct of a multicenter research project.

OHRP is aware that many IRBs require investigators to submit final closeout reports when a research study is completed or no longer involves human subjects. Since the HHS regulations at 45 CFR part 46 do not require submission of such reports, institutions are free to decide whether and when such reports are required and what their content should include.

L. Continuing Review is not Required for Exempt Human Subjects Research Projects

Human subjects research studies that qualify for exemption under 45 CFR 46.101(b) are exempt from all requirements of 45 CFR part 46, including the requirements related to continuing review. Investigators should follow the established institutional policies and procedures for determining whether proposed human subjects research projects are exempt. Once the determination has been made that a project is exempt, no continuing review of the project by the IRB is required under the HHS regulations at 45 CFR part 46.

However, if an investigator decides to modify an exempt human subjects research project in such a way that it would no longer qualify for exemption, the investigator must submit the modified research protocol to the IRB for review prior to implementation of the modified research project (45 CFR 46.103(b) and 46.109(a)).

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.

Appendix
Scenarios for Determining Continuing Review Dates

A. Determining the First Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting at the Time of Initial Review and Approved Without Conditions for One Year

- Scenario A: An IRB conducts initial review of a research project at a convened meeting on October 1, 2009 and approves the project for one year without requiring (a) any changes to protocol or informed consent documents, or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval would be October 1, 2009, and the expiration date of the initial approval period and the date by which the first continuing review must occur is one year after the date of the IRB meeting, that is, October 1, 2010.

B. Determining the *First* Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting at the Time of Initial Review and Approved with Conditions for One Year

- Scenario B1: An IRB conducts an initial review of a research project at a convened meeting on October 1, 2009, approves the project for one year, and requires that the investigator make minor changes to the protocol as a condition of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised protocol and determine whether the changes required by the IRB have been made. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The effective date of the initial IRB approval is November 1, 2009. When approving research for one year with conditions at the time of initial review, the IRB follows a procedure where the expiration date of the initial approval period is one year after the effective date of initial IRB approval (i.e., the date on which the IRB chairperson or any other individual(s) designated by the IRB has determined that the conditions of approval have been satisfied). Therefore, the expiration date of the initial approval period and the date by which the first continuing review must occur is November 1, 2010.

- Scenario B2: An IRB conducts an initial review of a research project at a convened meeting on October 1, 2009, approves the project for one year, and requires that the investigator make minor changes to the protocol as a condition of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised protocol and determine whether the changes required by the IRB have been made. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The effective date of the initial IRB approval is November 1, 2009. When approving research for one year with conditions at the time of initial review, the IRB follows a procedure where the expiration date of the initial approval period is one year from the date of the IRB meeting at which the research project initially was approved with conditions. Therefore, the expiration date of the initial approval period and the date by which the first continuing review must occur is October 1, 2010.

- Scenario B3: An IRB conducts initial review of a research project at a convened meeting on October 1, 2009, and has serious concerns regarding the study design. The IRB defers taking action on the project and requires that the investigator submit a revised protocol in order to secure approval at a future IRB meeting. At a convened meeting on

December 1, 2009, the IRB reviews a revised protocol, approves the research project for one year, and requires that the investigator make minor changes to the informed consent document and submit documentation of a co-investigator's hospital privileges as conditions of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, (a) the revised informed consent document to determine whether the changes required by the IRB have been made, and (b) the documentation of the co-investigator's hospital privileges. On December 15, 2009, the IRB chairperson reviews the revised informed consent document and documentation of the co-investigator's hospital privileges, and determines that the changes made by the investigator to the informed consent document and the documentation of the co-investigator's hospital privileges are satisfactory. The effective date of the initial IRB approval is December 15, 2009. When approving research for one year with conditions at the time of initial review, the IRB follows a procedure where the expiration date of the initial approval period is one year after that effective date of initial IRB approval (i.e., the date on which the IRB chairperson or any other individual(s) designated by the IRB has determined that the conditions of approval have been satisfied). Therefore, the expiration date of the initial approval period and date by which the first continuing review must occur is December 15, 2010.

NOTE: For all of the scenarios that follow, assume that when the IRB approves research for one year with conditions at the time of initial review, the IRB follows a procedure where the expiration date of the initial approval period is one year after that effective date of initial IRB approval (i.e., the date on which the IRB chairperson or any other individual(s) designated by the IRB has determined that the conditions of approval have been satisfied).

C. Determining the Date for the *Second and all Subsequent* Continuing Reviews for Research Reviewed by the IRB at Convened Meetings and Approved for One Year Intervals, Including How to Maintain a Fixed Anniversary Date for the Expiration of Annual IRB Approvals

- Scenario C1: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals and conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the project without conditions for another one-year period. The expiration date of the second approval period is October 1, 2011. The second continuing review must occur by October 1, 2011.

- Scenario C2: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB does not follow a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals and conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the project without conditions for another one-year period. The expiration date of the second approval period is September 15, 2011, and the second continuing review must occur by this date.

- Scenario C3: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals and conducts its first continuing review of the research project at a convened meeting on August 15, 2010 (i.e., more than 30 days before the initial IRB approval period expires) and re-approves the project without conditions for another one-year period. Because the first continuing review did not occur within 30 days before the IRB approval period expired, the expiration date of the second approval period is August 15, 2011, and the second continuing review must occur by this date.

- Scenario C4: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals and conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the research for another one-year period with the condition that the investigator makes a change to the protocol. On September 22, 2010, the IRB chairperson receives from the investigator a revised protocol, and verifies that the required change has been made. The expiration date of the second approval period is October 1, 2011, and the second continuing review must occur by this date.

- Scenario C5: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB does not follow a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals. The IRB conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the research for another one-year period with the condition that the investigator makes a change to the protocol. On September 22, 2010, the IRB chairperson receives from the investigator a revised protocol, and verifies that the required change has been made. The expiration date of the second approval period is September 15, 2011, and the second continuing review must occur by this date.

- Scenario C6: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals. The IRB conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the research for another one-year period with the condition that the investigator makes a change to the informed consent document within 60 days. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised informed consent document and determine whether the changes required by the IRB have been made. The IRB also specifies that no new subjects may be enrolled in the research until the IRB chairperson reviews the revised informed consent document and verifies that the required change has been made. On October 31, 2010, the IRB chairperson reviews the revised informed consent document and determines that the changes made by the investigator are satisfactory. Enrollment of new subjects may resume on October 31, 2010. The expiration date of the second approval period is October 1, 2011, and the second continuing review must occur by this date. Note that under this scenario, there is no lapse in IRB approval between October 1 and October 31, 2010, and during this time, the investigator is allowed to continue research activities involving already enrolled subjects.

- Scenario C7: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals. The IRB conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the research for another one-year period with the condition that within 60 days the investigator makes a change to the protocol by adding the administration of a new follow-up data collection procedure one year after the subjects began receiving the research intervention, for all subjects who have not yet reached that point. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised protocol and determine whether the change required by the IRB has been made. On October 31, 2010, the IRB chairperson receives and reviews the revised protocol and verifies that the investigator made the requested change. The expiration date of the second approval

period is October 1, 2011, and the second continuing review must occur by this date. Note that under this scenario, there is no lapse in IRB approval between October 1 and October 31, 2010, and during this time, the investigator is allowed to continue research activities involving already enrolled subjects and to enroll new subjects in the research.

- Scenario C8: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The investigator does not submit the necessary progress report for the first continuing review until October 31, 2010. As a result, IRB approval expired/lapsed on October 1, 2010, and all research activities involving human subjects must stop except in the limited circumstances described in section H below. The IRB conducts its first continuing review of the research project at a convened meeting on November 15, 2010 and re-approves the project without conditions for another one-year period. The expiration date of the second approval period could be as late as November 15, 2011, or the IRB could specify that the second IRB approval period expires on October 1, 2011 so as to retain the original anniversary date on which the first approval period expired. The second continuing review must occur by whichever date is specified by the IRB.

D. Determining the Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting and Approved for Less Than One Year

- Scenario D1: An IRB conducts initial review of a research project at a convened meeting on October 1, 2009 and approves the project for 6 months without requiring (a) any changes to the protocol or informed consent document(s), or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval is October 1, 2009, and the first continuing review must occur within six months of the date of the IRB meeting, that is, by April 1, 2010. The IRB conducts its first continuing review of the research project at a convened meeting on March 15, 2010 and re-approves the project without conditions for another six-month period. The IRB stipulates that the expiration date of the second approval period is October 1, 2010, and the second continuing review must occur by this date.

- Scenario D2: An IRB conducts initial review of a research project at a convened meeting on October 1, 2009, approves the project for 6 months, and requires that the investigator make minor changes to the protocol as a condition of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised protocol and determine whether the changes required by the IRB have been made. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The effective date of the initial IRB approval is November 1, 2009, and the first continuing review must occur within six months of that date, that is, by May 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals, and conducts its first continuing review of the research project at a convened meeting on April 15, 2010 and re-approves the project without conditions for one year. The expiration date of the second approval period is May 1, 2011, and the second continuing review must occur by this date.

- Scenario D3: At a convened meeting on October 1, 2009, an IRB conducts initial review of a research project that is a high-risk phase I clinical trial involving healthy subjects and approves the project for 6 months or until the first three subjects have enrolled and received the study intervention – whichever is sooner – without requiring (a) any changes to the protocol or informed consent document(s), or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval is October 1, 2009, and the first continuing review must occur within six months of the date of the IRB meeting, that is, by April 1, 2010, or after the first three subjects have enrolled and received the study intervention, whichever is sooner. The third subject is enrolled and receives the study intervention on February 1, 2010. No further subjects can be enrolled in the project until the IRB conducts continuing review at a convened meeting and re-approves the research. The IRB conducts its first continuing review of

the research project at a convened meeting on February 15, 2010 and re-approves the project without conditions for another six-month period or until the next three subjects have enrolled and received the study intervention – whichever is sooner. The next continuing review must occur by August 15, 2010, or after the next three subjects have enrolled and received the study intervention, whichever is sooner.

E. Determining the Continuing Review Date for Research Reviewed by the IRB Under an Expedited Review Procedure

- Scenario E1: An IRB chairperson conducts initial review of a research project under an expedited review procedure on October 1, 2009 and approves the project for one year without requiring (a) any changes to the protocol or informed consent document, or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval is October 1, 2009, and the first continuing review must occur within one year of that date, that is, by October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals, and the IRB chairperson conducts the first continuing review of the research project under an expedited review procedure on September 15, 2010 and re-approves the project without conditions for one year. The expiration date of the second approval period is October 1, 2011, and the second continuing review must occur by this date.

- Scenario E2: An IRB chairperson conducts initial review of a research project under an expedited review procedure on October 1, 2009, approves the project for one year, and requires that the investigator make minor changes to the protocol as a condition of the IRB's approval. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The date of the initial IRB approval is November 1, 2009, and the first continuing review must occur within one year of that date, that is, by November 1, 2010. The IRB does not follow a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals, and the IRB chairperson conducts the first continuing review under an expedited review procedure on October 15, 2010, and re-approves the research for another one-year period with the condition that the investigator makes a specific word change to the informed consent document. The IRB chairperson designates the IRB administrator, who is not an IRB member, to review the revised informed consent document and confirm that the required change was made. On October 22, 2010, the IRB administrator receives from the investigator a revised informed consent document, and verifies that the required change has been made. The expiration date of the second approval period is October 15, 2011, and the second continuing review must occur by this date.

For the sake of simplification, in this sentence and many subsequent sentences, OHRP has used the singular noun "investigator" when the plural noun "investigators" may also be appropriate.

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);
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.html.) 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.

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Guidance for IRBs, Clinical Investigators, and Sponsors

IRB Continuing Review after Clinical Investigation Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)

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Guidance for IRBs, Clinical Investigators, and Sponsors[1] IRB Continuing Review after Clinical Investigation Approval

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.

I. INTRODUCTION

This guidance is intended to assist institutional review boards (IRBs) in carrying out their continuing review responsibility under 21 CFR 56.108(a) and 56.109(f) by providing recommendations regarding the criteria, process, and frequency of continuing review to assure the protection of the rights and welfare of human subjects enrolled in clinical investigations. This guidance should also help clinical investigators and sponsors better understand their responsibilities related to continuing review. This document supersedes the Information Sheet, *Continuing Review After Study Approval* (September 1998, Office of Health Affairs, FDA). To enhance human subject protection and reduce regulatory burden, the Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP) and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This guidance document was developed as a part of these efforts.[2]

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.

[1] This guidance has been prepared by FDA's Institutional Review Board Working Group, which includes representatives from FDA's Office of the Commissioner, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).

[2] For studies subject to 45 CFR part 46 (i.e., studies that are funded, conducted, or supported by HHS, OHRP has issued guidance on IRB continuing review. See "Guidance on IRB Continuing Review of Research," http://www.hhs.gov/ohrp/policy/continuingreview2010.pdf and "Guidance on IRB Approval of Research with Conditions," http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html.

II. BACKGROUND

FDA's IRB regulations were first issued in 1981, when the single investigator-single site study was the norm for clinical trials, and reporting requirements to IRBs were almost entirely and appropriately fulfilled by the investigator, who was in a position to know about all aspects of a study. Since that time, multi-site studies have become commonplace. Although an individual investigator informs the IRB about events at the investigator's site, the investigator and IRB may not generally be well-informed about the far greater body of data reflecting events across all study sites. IRB review and oversight of such research has consequently become more challenging. Given the changes in the way clinical studies are conducted, this guidance makes specific recommendations to assist IRBs in conducting continuing review.

III. DISCUSSION

With respect to continuing review, FDA's regulations require an IRB to develop and follow written procedures for:

- Conducting continuing review of research at intervals appropriate to the degree of risk, but not less than once a year (21 CFR 56.108(a)(1) and 56.109(f));

- Determining which clinical investigations require review more often than annually (21 CFR 56.108(a)(2));

- Determining which clinical investigations need verification from sources other than the clinical investigator that no material changes in the research have occurred since the previous IRB review (21 CFR 56.108(a)(2)); and

- Ensuring prompt reporting to the IRB of changes in research activity and for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 56.108(a)(3) and (4)).

The purpose of written procedures is to ensure that IRBs have a framework for periodically reviewing the conduct of clinical investigations of FDA-regulated products (e.g., drugs, including biologics, and devices). FDA's regulations do not provide specific instructions to IRBs on how to set up their own rules. The regulations allow institutions and IRBs to develop their own procedures or additional requirements as appropriate to the IRB's needs.

While a clinical investigation is ongoing, IRBs review and consider changes in research as they are received, including protocol amendments.[3] They also review changes to the informed consent document,[4] reports from investigators or sponsors of unanticipated problems,[5] and other

[3] See 21 CFR 56.108(a)(3) and (4), 56.109(a), and 56.110(b)(2).
[4] See 21 CFR 56.109(b).
[5] See 21 CFR 56.108(b)(1).

information about the investigation. IRB review of a proposed change in research during the period for which approval is authorized does not constitute continuing review of the research as a whole, and thus does not extend the date by which continuing review must occur (e.g., beyond one year from the effective date of the initial approval or the most recent continuing review approval). Although an IRB may become familiar with various individual aspects of the study's conduct, such familiarity does not relieve the IRB of the responsibility to conduct continuing review, which provides an opportunity to reassess the totality of the study and assure that, among other things, risks to subjects are (1) minimized, and (2) still reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result (21 CFR 56.111(a)(1) and (2)).

This formal review of the research effort, as required under 21 CFR 56.109(f), is the subject of this guidance. An IRB must review previously approved research at least once a year (21 CFR 56.109(f)). Review must be conducted at convened meetings at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas, unless the research qualifies for review through an expedited process (21 CFR 56.108(c) and 56.110). See Section III.D. of this guidance for more information on the application of expedited review procedures to continuing review.

IRBs involved in multi-site studies may find it difficult to conduct a thorough review with data solely from the site(s) under their purview and may need to obtain study-wide information. Sponsors are in the unique position of having information for the entire study[6] and may provide it to investigators, who in turn provide it to the IRBs. FDA's regulations do not prohibit sponsors from providing study-wide information directly to IRBs.[7] FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful study-wide information, particularly when doing so may assist IRBs in reviewing the studies and protecting subjects.

One way to enable a useful continuing review of multi-site studies while reducing or eliminating duplication of effort is through the use of cooperative review agreements or other mechanisms (e.g., using a centralized IRB review process), in accordance with 21 CFR 56.114. Cooperative agreements may vary with respect to how continuing review will be carried out. For example, some agreements may designate a specific IRB as having primary responsibility for continuing review of an investigation.[8] Other agreements may assign responsibility for local issues to the institution's IRB, but assign the remaining aspects of continuing review to a central IRB.

Whatever the arrangement, the IRB(s) responsible for continuing review of multi-site studies may find it helpful to obtain and review information across the entire study. For additional discussion, see Section III.B. of this guidance.

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[6] See FDA's Guidance for Industry, "Adverse Event Reporting to IRBs – Improving Human Subject Protection," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.

[7] Note that FDA's regulations for device studies specifically assign general responsibility to sponsors "…for ensuring IRB review and approval are obtained and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation…" 21 CFR 812.40.

[8] See FDA's Guidance for Industry, "Using a Centralized IRB Review Process in Multicenter Clinical Trials," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080606.pdf.

A. Criteria for Approving Research During Continuing Review

FDA regulations set forth the criteria for IRB approval of research (21 CFR 56.111). These criteria apply to both initial review and continuing review. In order to approve research, the IRB must determine that all of following requirements are satisfied:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result;
- Selection of subjects is equitable;
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented;
- Where appropriate, the research plan adequately provides for monitoring the data collected to ensure the safety of subjects;
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
- Appropriate additional safeguards are included to protect vulnerable subjects; and
- Where the study involves children, the research complies with 21 CFR part 50, Subpart D.

The IRB makes its continuing review determination by considering whether any new information is available that would affect the IRB's prior finding that the research meets the criteria in 21 CFR 56.111. IRBs have authority to disapprove or require modifications in (to secure re-approval of) a research activity that does not meet any of the above criteria (e.g., the full study or any part thereof, such as changes to the protocol, advertisements; 21 CFR 56.109(a))

B. Process for Conducting Continuing Review

Continuing review takes place at a convened meeting of the IRB, unless it meets the criteria for expedited review under 21 CFR 56.110. (See 21 CFR 56.108(c) and Section III.D. of this guidance.) The IRB is required to review the research (21 CFR 56.109(f)) and must maintain records of its continuing review activities, including minutes of meetings at which such activities are undertaken (21 CFR 56.115(a)(2) and (3)). The minutes must be in sufficient detail to show actions taken by the IRB, and the vote on these actions, and to summarize the discussion of controverted issues and their resolution (21 CFR 56.115(a)(2)). For research to be approved, a majority of IRB members present at a meeting must approve it (21 CFR 56.108(c)).

The IRB must ensure that a member does not participate in the IRB's continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (21 CFR 56.107(e)). Meeting minutes must reflect meeting attendance, the votes taken, and a summary of the discussion and resolution of controverted issues, and should provide confirmation that conflicted members did not participate in the IRB's continuing review of their studies (21 CFR 56.115((a)(2)). FDA recommends that IRB members with a conflicting interest in a project recuse themselves by leaving the meeting room when the IRB conducts continuing review of that project, except when requested by the IRB to be present to provide information.

This IRB member recusal should be noted in the minutes of the IRB meeting when recording votes on IRB actions.

An IRB must maintain and follow written procedures for the continuing review of research (21 CFR 56.108(a)(1) and 56.115(a)(6)). In developing procedures for continuing review, the IRB should consider the use of templates, checklists, or other tools to standardize the request for information or list of materials to be provided to the IRB at the time of continuing review.

Investigators are responsible for ensuring that studies they conduct comply with applicable regulatory requirements.[9] To ensure that the reviewing IRB can carry out its review prior to the expiration date of the current IRB approval, investigators should follow the IRB's policies and procedures for continuing IRB review of research (procedures required by 21 CFR 56.108(a)(1)), in particular by submitting materials and information required by the IRB. FDA encourages IRBs to make investigators aware of the IRB's procedures, for example, by enclosing a copy in correspondence informing the investigator of the IRB's decisions, or posting the information on a website.

FDA recommends that the IRB's written procedures call for submission of the following information for consideration by the IRB in continuing review, if not already available to the IRB as part of the existing IRB records for the research[10]:

- A written progress report/brief project summary that includes the following or references other documents made available to the IRB:
    - The number of subjects accrued; (For multi-site studies, the number of subjects accrued at the local site and the number accrued study-wide, if available, should be provided.)
    - A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review;
    - Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research; (Note that FDA does not expect the IRB to perform an independent review of the relevant scientific literature related to a particular research project undergoing continuing review.)
    - A summary of any unanticipated problems.[11] In many cases, such a summary could be a brief statement that there have been no unanticipated problems (i.e., adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and Investigator's Brochure (if applicable));

[9] See 21 CFR 312.53(c)(1)(vii), 312.60, 312.66, 812.36(c)(viii), 812.100, 812.110(b), 812.40, and 812.43(c)(4)(i).
[10] Some of this information may come from the sponsor, who would have access to data across all study sites. Sponsors may provide information directly to IRBs or to the clinical investigators who in turn would share it with the IRBs.
[11] IRB procedures must ensure that there is prompt reporting to the IRB of unanticipated problems involving risks to human subjects or others (21 CFR 56.108(b)(1)). See "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs--Improving Human Subject Protection," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.

  - A summary of any subject withdrawals from the research since the last IRB review, and the reasons for withdrawal, if known; and
  - A summary of any complaints about the research from subjects enrolled at the local site since the last IRB review;
- The latest version of the protocol and sample informed consent document(s) in use at the site;
- Any proposed modifications to the informed consent document or protocol;
- The current Investigator's Brochure, if any, including any modifications;
- Any other significant information related to subject risks, such as the most recent report, if any, from data monitoring committees (DMCs);[12] (Additionally, it may be useful for sponsors to ensure that IRBs are informed when DMCs have met, even when no problems have been identified and the DMC has recommended continuation of the study as designed. This information can be transmitted either by the investigator or directly by the sponsor.) and
- Aggregate information about relevant regulatory actions occurring since the last review that could affect safety and risk assessments (e.g., withdrawal or suspension from marketing in any country on the basis of safety, reports of recalls and device disposition required by 21 CFR 812.150(b)(6)).

If the information listed above is not already included in an existing report (prepared by the sponsor for some other purpose or entity),[13] then a separate progress report should be prepared and submitted to the IRB for continuing review of the study. However, if the information listed above is included in an existing report then this report may be re-purposed and submitted to the IRB at the time of continuing review of the study. For example, as noted above, sponsors of investigational drug studies are required by 21 CFR 312.33 to submit annual reports to FDA on the progress of their studies. Sponsors of investigational device studies are already required to provide progress reports to all reviewing IRBs at least annually (21 CFR 812.150(b)(5)).

Submitting the annual report for drug studies or the progress report for device studies is one mechanism of providing the IRB with pertinent information for consideration at the time of continuing review. These reports, with little or no modification, usually will contain the information listed above, and could be redacted such that proprietary information and information about other studies unrelated to the continuing review are removed prior to submission to the IRB.

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[12] See FDA's "Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf .

[13] FDA received comments that international regulatory authorities require periodic aggregate reports be submitted to independent ethics committees (IECs). Because these reports are already being generated and are written for IRBs/IECs for global research, it was suggested that these reports could be used as a means of reducing burdens and harmonizing requirements for multinational trials, while providing necessary information to IRBs. [See Docket # FDA-2009-D-0605, accessible on www.regulations.gov .] FDA does not object to this practice. For clinical investigations involving drugs and biologics, IRBs could ask for the Development Safety Update Report (DSUR) Executive Summary, if available. The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it has a marketing approval. See ICH "Guidance for Industry, E2F Development Safety Update Report," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf .

When an IRB is conducting continuing review, the IRB should be knowledgeable about the investigation, including materials associated with previous ad hoc or scheduled reviews related to protocol amendments, the Investigator's Brochure, or unanticipated problems involving risks to subjects. The IRB file, including relevant IRB meeting minutes, should be made available to IRB members prior to the meeting at which continuing review will be conducted. The file should also be accessible during the meeting at which the research is discussed to allow members to resolve any questions that may arise.

For multi-site studies, IRBs should obtain study-wide information, DMC reports, and any other information about the test article that would be relevant to the IRB's continuing review. The investigator can provide this information to the IRB, but may first need to obtain the information from the sponsor. The investigator and sponsor can agree that the sponsor will submit this information directly to the IRB. Sponsors are in the unique position of having information across all study sites, interim assessments by DMCs, and safety information obtained or otherwise received from any source, foreign or domestic (e.g., information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, relevant articles from published or unpublished sources, reports from non-U.S. regulatory authorities), that could assist the IRB in reviewing the study and protecting subjects.[14]

The IRB that conducted the initial review of a study may be best suited to conduct continuing review of the study because of its familiarity with the study and/or previous review(s). However, FDA is aware that some institutions have designated one or more IRBs for the sole purpose of conducting continuing review. It is permissible under FDA regulations for an IRB other than the IRB that conducted the initial review to perform continuing review of a study, as long as the IRB conducting the continuing review satisfies regulatory requirements such as the IRB membership requirements under 21 CFR 56.107 and fulfills the regulatory requirements for conducting continuing review. The IRB conducting continuing review should also have access to all prior relevant IRB records.

FDA recommends that, whenever possible, an IRB's written procedures include measures intended to reduce burdens and allow the IRB to efficiently accomplish its continuing review workload. For example, IRB written procedures may allow:

- appropriately trained staff to perform preliminary review of study materials to assure that the documents necessary for continuing review have been submitted and the file is complete; and
- one or more experienced IRB members to perform primary review of the continuing review file and report, summarize changes or critical issues for the other members, and lead the discussion at a convened meeting (e.g., "no/only minimal changes since the last continuing review date"; "AE reports are of the type and frequency as described in the current Investigator's Brochure or informed consent document; no changes are necessary at this time").

[14] See "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs--Improving Human Subject Protection," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf .

FDA is aware of instances in which an IRB has allowed voting on groups of studies (sometimes called "block voting"). If block voting is to be used, FDA recommends that the IRB's procedures provide IRB members with ample opportunity to carefully consider and discuss studies individually and express concerns before the voting occurs. The IRB's procedures should allow members to vote "yes" on some studies, "no" on others, and abstain on others.

C. Key Topics to Consider During Continuing Review

When conducting continuing review, the IRB should start with the assumption that the research, as previously approved, satisfied all of the criteria under 21 CFR 56.111. The IRB should focus on any new information provided by the investigator or sponsor, or otherwise available to the IRB, that may alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document. If the IRB determines that a research activity no longer meets the criteria for approval under 21 CFR 56.111, the IRB is not permitted to reapprove it, but may either disapprove it or require modifications in order to secure re-approval (21 CFR 56.109(a)).

As discussed below, when conducting continuing review and evaluating whether research continues to satisfy the criteria for IRB approval of research, IRBs should pay particular attention to the following areas: 1) Risk Assessment; 2) Adequacy of Informed Consent; 3) Local Issues, and 4) Trial Progress.

The amount of time the IRB spends on the continuing review of a particular study will vary depending on the nature and complexity of the research, the amount and type of new information presented to the IRB and whether the investigator is seeking approval of substantive changes to the research protocol or informed consent document. For many studies, continuing review can be fairly straightforward, and the IRB should be able to complete its deliberations and review promptly.

1. Risk Assessment

During continuing review, the IRB must determine that the criteria necessary for IRB approval under 21 CFR 56.111 are met. This includes determining whether information provided at the time of continuing review would alter either the conclusion 1) that the risks to subjects are minimized, or 2) that the risks to subjects are reasonable in relation to anticipated benefits (21 CFR 56.111(a)(1) and (2)). The IRB's review procedures under 21 CFR 56.108 should ensure that the IRB will consider any new information that has been received since the date that the IRB last reviewed the study (e.g., sponsor's annual report, periodic aggregate reports, any analysis by the sponsor performed since then). See Section III.B. of this guidance.

2. Adequacy of Informed Consent

At the time of continuing review, the IRB should review the informed consent document to verify that the site is using the most recently approved version, and evaluate whether this document contains accurate, up-to-date information about the study. FDA recommends use of

methods that will allow the IRB to readily recognize the most current version of the informed consent document, for example, using date stamps or initialing and dating documents to indicate when a version was approved.

When reviewing informed consent document(s), the IRB must evaluate whether the currently approved consent document or any revised consent document proposed for approval contains accurate, up-to-date information about the study (i.e., meets the criteria in 21 CFR 50.25, including the requirement to include any reasonably foreseeable risks. See 21 CFR 56.109(b) and 56.111(a)(4-5)). In particular, the IRB's continuing review may reveal new risk information that will require updating of informed consent materials in order to satisfy these requirements. Although the IRB may have reviewed the informed consent document when new information or a protocol amendment was submitted to the IRB, such review would not eliminate the need to review the informed consent document during continuing review. In addition, the IRB should ensure that information about any significant new findings identified since the last continuing review that may relate to the subjects' willingness to continue participation will be provided to enrolled subjects (e.g., important toxicity information, or adverse event information identified during analysis of reports across all sites).

In multi-site studies, a central IRB may be reviewing the adequacy of informed consent, depending on the agreement between the local IRB and the central IRB. The central IRB may accomplish this function by reviewing a model/template informed consent document or site-specific informed consent documents in use at one or more, or even all, individual sites.[15]

3. Local Issues

The reviewing IRB should consider local concerns during both initial and continuing review, including:

- Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, medical license; involvement in numerous clinical trials);
- Evaluation, investigation, and resolution of complaints related to the research;
- Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and regulations, applicable state and local law, or standards of professional conduct or practice;
- Reports from third party observation of the research (including the informed consent process) carried out under 21 CFR 56.109(f); and
- Investigator concerns about trial conduct at the local site (e.g., study coordinator ineffectiveness, inability of subjects to understand sections of the informed consent document required by institutional policies).

If review responsibilities for a study are shared under a cooperative agreement, the written agreement should identify the responsibilities covered by the agreement and who is responsible

[15] See "Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080606.pdf .

for them. If a central IRB is responsible for continuing review including evaluation of local issues, the central IRB's procedures should ensure that local issues are addressed. For example, the central IRB may ask the investigator for more information related to subject withdrawals, or decide to visit specific sites to determine the facts in order to assure the safety and welfare of study subjects.

4. Trial Progress

Total Subject Enrollment. The sponsor has primary responsibility for monitoring the study. However, the IRB's responsibility to protect human subjects should include the IRB's review of trial progress. For example, expected rates of enrollment and dropout are generally identified for most studies. A marked difference between the actual and expected rates of enrollment or dropout, either at an individual site or in the study as a whole, may indicate a problem requiring further investigation.

As part of its initial review, the IRB will have approved the protocol, which typically includes the number of subjects expected to be enrolled at a particular site. An investigator who enrolls more subjects than the number allowed at that site may have violated the study protocol or conditions set by the IRB or FDA.

Information about the number of subjects enrolled in the overall study may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the approved protocol. If enrollment in the study as a whole is too low (either because subject enrollment is too low or subject withdrawal is too high), there may not be justification to continue exposing subjects to the risks of the test article because the study itself may no longer be expected to provide sufficient data to answer the scientific question at hand. (See 21 CFR 56.111(a)(2).)

To address low enrollment issues, an IRB may recommend that the reasons behind the lagging enrollment be explored and appropriate steps be taken to remedy the situation (e.g., proposals for modification of recruitment practices, adjustment of inclusion criteria, evaluation of reasons for excessive withdrawal). In a multi-site study, participating sites might be enrolling subjects at different times. In this case, information about enrollment across all sites may reaffirm that there is sufficient rationale to continue a clinical investigation at an individual site despite low local enrollment. IRBs should note that once the study is completely enrolled, the study should not be unduly prolonged.[16]

Subject Withdrawals. Subjects may withdraw from studies for various reasons (e.g., serious adverse events, conflicts with site staff, transportation problems).

IRB continuing review procedures should provide for review of

- the number of subjects who withdrew from the research at the local site as compared to other sites, and
- a summary of the reasons for the local withdrawals.

[16] See 21 CFR 312.7(c) and 21 CFR 812.7(c).

Information about subject withdrawals may be available in IRB or institutional files, or obtained from other sources (e.g., complaint files, sponsor, clinical investigator, contract research organization (CRO)). IRB review of this information may shed light on problems related to the conduct of the research at the local site.

D. When Expedited Review Procedures May Be Used for Continuing Review

21 CFR 56.110(b) allows for expedited review of research that is included in the list of categories published in the Federal Register[17] and is found to involve no more than minimal risk. This regulation permits continuing review to be conducted using expedited procedures if these requirements are met.

Where a study qualifies for expedited review, review may be conducted by the IRB chairperson or one or more experienced reviewers designated by the chairperson from among the IRB members, who then advise all members of the review decisions made. (See 21 CFR 56.110(b) and (c).)

Disapproval of a study at the time of continuing review can only occur at a convened meeting, not by the expedited review process. The IRB chairperson or his/her designee can approve a study or require modification of the study to secure its approval, but may not disapprove research using the expedited procedures (21 CFR 56.110(b)).

The current list of research eligible for expedited review identifies nine categories of research, the last two of which (8 and 9) apply only to continuing review of research previously approved by the convened IRB (that is, not earlier approved under expedited review). These two categories will be discussed further below. (See Appendix for the list of categories of research eligible for expedited IRB review.)

Under the current list, research that meets the requirements of categories (1) through (7) at the time of review may qualify for expedited review whether that is initial or continuing review. In general, research that qualified for expedited review under one of these seven categories at the time of initial review will continue to qualify for expedited continuing review. However, IRBs should be aware that a study previously approved under an expedited review procedure, in some circumstances, will need to undergo continuing review by the IRB at a convened meeting. For example, a study that previously qualified for expedited review under categories (1)-(7) may require review by the convened IRB if information indicates that the study no longer fits that category or no longer can be said to involve no more than minimal risk. Conversely, research that previously required review (either initial or continuing) by an IRB at a convened meeting may become eligible for expedited review at the time of continuing review, for example if it meets the requirements of categories (8) or (9).

[17] See Appendix for text of 63 FR 60353, November 9, 1998, or at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed.pdf .

1. Expedited Review Category (8)

Category (8), which applies only to continuing review, provides that continuing review of research previously approved by the convened IRB (e.g., not originally subject to expedited review) may be eligible for expedited review:

(a) Where
  (i) the research is permanently closed to the enrollment of new subjects;
  (ii) all subjects have completed all research-related interventions; and
  (iii) the research remains active only for long-term follow-up of subjects; or
(b) Where no subjects have been enrolled and no additional risks have been identified; or
(c) Where the remaining research activities are limited to data analysis.[18]

For a multi-site study, an expedited review procedure may be used by an IRB whenever the conditions of category (8)(a), (b) or (c) are satisfied for the study under continuing review.

For a multi-site study, the various sites will likely have different start dates and rates of enrollment and, thus, may be at different progress points in the trial. As a result, the IRBs for sites that meet the criteria in Expedited Review Category (8) may conduct continuing review using an expedited review procedure, whereas IRBs for sites that do not meet those criteria would need to conduct continuing review of the study at a convened meeting. The IRBs for site(s) performing an ongoing activity such as long-term follow-up or data analysis (e.g., the site operating the coordinating center or statistical center for the study) would need to ensure that continuing review of the study for those sites occurs at least annually. Other sites in a multi-site study may have completed the study and, having no further data analysis or other responsibility in the trial, may be closed out; continuing review for these sites would no longer be necessary.

For a multi-site study in which there is a central IRB, there should be a written agreement delineating the responsibilities of the central IRB and local IRBs.[19] Depending on the terms of any review agreement(s) between the local IRB(s) and the central IRB, it may be possible for the central IRB to provide continuing review for the study for more than one site using expedited review procedures.

Expedited review category (8)(a) and the meaning of "long-term follow-up"

Under expedited review category (8)(a), FDA interprets "long-term follow-up" to include:

- Research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys); and
- Collection of follow-up data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research protocol.

[18] See 63 FR 60356, November 9, 1998, available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed.pdf.
[19] See "Guidance for Industry - Using a Centralized IRB Review Process in Multicenter Clinical Trials," http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm .

In contrast, FDA interprets "long-term follow-up" to exclude:

- Research *interventions* that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.

Of note, some studies that are not eligible for expedited review under category (8)(a) at the time of continuing review may be eligible for expedited review under one of the other expedited review categories. For example, if a study's only remaining activity involves long-term follow-up of subjects by drawing 15 ml of blood once annually for a test that is not part of routine clinical practice, such research would not be eligible for expedited review under category (8)(a), but might be eligible for expedited review under category (2).

Expedited review category (8)(b)

IRBs conducting continuing review should be aware that if a study previously received expedited continuing review under category (8)(b), but has now begun enrolling subjects, the study may need to be referred for review by the IRB at a convened meeting. The criterion that "no additional risks have been identified" is interpreted by FDA to mean that neither the investigator nor the IRB has identified any additional risks in the research from any relevant source[20] since the IRB's most recent prior review.

Expedited review category (8)(c)

FDA notes that the process for conducting continuing review of research eligible under expedited review category (8)(c) can be accomplished through a simple, abbreviated process. For example, if the study is no longer enrolling subjects, all subjects have completed all protocol required visits, and no new data is being collected, and the investigator's sole activity is data analysis, the investigator, as part of the continuing review process, could provide to the IRB the following statement regarding the research: "The study only involves data analysis, which is proceeding in accordance with the IRB-approved research protocol, and there are no problems to report." This statement could be provided by email or as part of a standard continuing review application form. Upon receipt of such a statement from the investigator, the IRB chairperson, or other member(s) designated by the chairperson, under the expedited review procedure, may approve continuation of the research project for another year without further deliberation or review.

Once the data collection from all trial sites is complete and the overall study results database has been locked and the only remaining activity is analysis of the aggregate data by the study sponsor, further continuing review of the research is generally no longer required.

[20] For example, "any relevant source" would include a review of scientific literature or adverse event reports by the IRB or investigator, as well as communication with FDA or the sponsor.

2. Expedited Review Category (9)

Similar to review category (1)[21] for initial review, under category (9), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug (IND) application or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and
- No additional risks have been identified.

With regard to the third condition, the IRB at a convened meeting must have determined that either (a) the research project as a whole involved no more than minimal risk, or (b) the remaining research activities present no more than minimal risk to human subjects. With regard to multi-site studies, the fourth condition, that no additional risks have been identified, is interpreted to mean that neither the investigator nor the IRB at a particular institution has identified any additional risks of the research based on information from any other institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.

E. Frequency of Continuing Review

Under 21 CFR 56.108(a)(2) and 56.109(f), the IRB must determine the frequency of continuing review for each clinical investigation to ensure the continued protection of the rights and welfare of research subjects. FDA regulations at 21 CFR 56.109(f) require an IRB to conduct continuing review of research at intervals appropriate to the degree of risk posed to the subjects, but not less than once a year.

More frequent review (i.e., more frequently than once per year) is appropriate, for example, when the risks to subjects require close monitoring. The IRB should consider the factors set forth below when deciding on an appropriate interval for continuing review. These factors should be outlined in the IRB's written procedures for deciding on the frequency of continuing review:

- The nature of and any risks posed by the clinical investigation;
- The degree of uncertainty regarding the risks involved;

[21] Category 1 research addresses "(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met: (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling." (63 FR 60353, at 60355, November 9, 1998)

- The vulnerability of the subject population;
- The experience of the clinical investigator in conducting clinical research;
- The IRB's previous experience with that investigator and/or sponsor (e.g., compliance history, previous problems with the investigator obtaining informed consent, prior complaints from subjects about the investigator);
- The projected rate of enrollment; and
- Whether the study involve novel therapies.

At the time of initial approval of the study, FDA recommends that the IRB notify the investigator of the interval at which continuing review will occur (at least annually) and the date by which continuing review must occur. Similarly, at the time of continuing review, the IRB should consider whether the current frequency of continuing review for the study is adequate or should be adjusted. In addition to specifying a time interval, the IRB may also specify a subject enrollment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the IRB might require that continuing review occur either in 6 months or after 5 subjects have been enrolled, whichever occurs first. However, if the continuing review interval is described in relation to a subject enrollment number, it must at a minimum also provide for continuing review annually, regardless of the number of subjects enrolled at that time; it is therefore not acceptable to describe the review interval solely in relation to a number of subjects enrolled. The minutes of IRB meetings should clearly document the approval period (continuing review interval).

The IRB's determinations regarding the approval of research must be communicated to the investigator in writing (21 CFR 56.109(e)). This written determination should also notify the investigator of the required interval for, and expected date of, continuing review.

F. Determining the Effective Date of Initial IRB Approval and the Dates for Continuing Review

Continuing review must occur at intervals appropriate to the degree of risk, but not less frequently than once per year (21 CFR 56.109(f)). IRBs should establish written procedures for informing investigators of the FDA's regulations and the IRB's own policies and procedures on continuing review requirements. (See 21 CFR 56.108(a)(1) & (2).) This applies whether a study is reviewed by the convened IRB or through an expedited process.

The IRB's written procedures should describe how the IRB determines the effective date of approval for the study and how the date and period of approval will be communicated to the clinical investigator.

1. When the IRB Reviews and Initially Approves Research Without Conditions at a Convened Meeting

When the IRB conducts the initial review of a study at a convened meeting and approves the research for one year *without* requiring either (a) changes to the protocol or informed consent document(s), or (b) submission of clarifications or additional documents, the effective date of the initial approval is the date of that IRB meeting. In such circumstances, the expiration date of the

initial approval period and the date by which the **first** continuing review must occur may be as late as one year after the date of the IRB meeting at which the research initially was approved (21 CFR 56.109(f)).

2. When the IRB Reviews and Initially Approves Research With Conditions at a Convened IRB Meeting Without Requiring Further Review at a Subsequent Convened Meeting

A much more common scenario is when an IRB conducting the initial review of a research project at a convened meeting takes the following set of actions:

- Approves the project for one year;
- As a condition of approval, requires 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 regulations; and
- Directs that the IRB chairperson (or other individual(s) designated by the IRB) review and determine on behalf of the IRB whether the changes, clarifications, and/or additional documents to be submitted by the investigator(s) are satisfactory.

When the IRB reviews and approves research ***with conditions*** at a convened IRB meeting without requiring further review at a subsequent convened meeting, 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 all changes to the protocol or informed consent documents, or any other responsive materials, required by the IRB from the investigators. In such circumstances, the expiration date of the initial approval period, which is the date by which the **first** continuing review must occur, may be as late as one year after that effective date of initial IRB approval (see 21 CFR 56.109(f)). (However, an IRB may choose to set the expiration date of the initial approval period at one year from the date of the IRB meeting at which the research project initially was approved with conditions.)

The IRB records must include documentation of the date when the IRB chairperson (or other individual(s) designated by the IRB) determined that all conditions of IRB approval have been satisfied and the approval becomes effective, and the expiration date of the initial IRB approval (i.e., the date by which the first continuing review must occur; see 21 CFR 56.115(a)).

3. Determining the Date for the Second and all Subsequent Continuing Reviews for Research Reviewed by the IRB at Convened Meetings and Approved for One Year Intervals, Including How to Maintain a Fixed Anniversary Date for the Expiration of Annual IRB Approvals

An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (21 CFR 56.109(f)). Given this requirement, it is important to recognize that the use of the "effective date" of IRB approval (i.e., the date on which the IRB chairperson or any other individual(s) designated by the IRB determined that the conditions of

approval have been satisfied) – as opposed to the date of the convened meeting at which the IRB approved a research study with conditions as described above – to determine the latest permissible date for continuing review ***only applies to the first continuing review.***

For all subsequent continuing reviews of research (i.e., the date for the second and all subsequent continuing reviews), if the IRB does *not* follow a procedure for maintaining fixed anniversary dates, the date of the convened meeting when the IRB conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

FDA recognizes the logistical advantages of keeping the expiration date of the IRB approval period constant from year to year throughout the life of the research. Therefore, when (a) the IRB grants approval for one year at the time of each continuing review, and (b) the IRB performs continuing review and re-approves (with or without conditions) the research within 30 days ***before*** the IRB approval period expires, the IRB may retain the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period. IRBs that adopt a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals should include a description of this procedure in their written procedures.

If the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, and the investigator works to promptly address and fulfill those conditions, FDA does not intend to object if the investigator needs some additional time, beyond the expiration date of the preceding IRB approval period, to satisfy some or all of the IRB's conditions. FDA would not expect the IRB to report such situations to the Agency.

The same guidelines for determining the continuing review dates would apply when the IRB determines that research must undergo continuing review more often than annually and when the IRB reviews and approves research under an expedited review procedure, in accordance with 21 CFR 56.110.

At the time of continuing review, the IRB must consider whether the current frequency of continuing review for the study is appropriate to the degree of risk or should be adjusted (21 CFR 56.109(f)). For example, if the IRB initially approved a research study for a period of a year and at the first annual continuing review determined that the risks posed to the subjects have increased significantly, the IRB might re-approve the project after determining that the criteria for approval under 21 CFR 56.111 remain satisfied, but require that the next continuing review occur in 6 months.

FDA recommends that the IRB's written procedures provide for sufficient advance notice to the investigator to ensure that the requirements for continuing review, by the anniversary or other date identified for the next continuing review, are met. The IRB should also develop administrative procedures to ensure that continuing review meetings are not only scheduled but occur before the necessary date and may use a tracking system to minimize any unintended expiration of IRB approval. FDA cautions, however, that if investigators submit materials for continuing review too far in advance of the expiration date of the IRB approval, the materials

may not reflect the current status of the study by the time that continuing review actually takes place. The IRB therefore should work to link as closely in time as possible: 1) the receipt by the IRB of continuing review materials; 2) the review of those materials by the IRB; and 3) the impending expiration date for IRB approval. Nevertheless, it is the investigator's responsibility to ensure that the study complies with applicable regulations.[22] Therefore, to ensure that IRB approval is maintained (without which the study cannot continue), the investigator should provide the information the IRB needs to perform its continuing review function in a timely and complete manner, whether or not the IRB provides any reminders.

Review of an amendment to a protocol during the period for which approval is authorized does not constitute continuing review of the study as a whole, and thus does not extend the date by which continuing review must occur (i.e., not more than one year from the original approval date or most recent continuing review approval date).

G. Communicating the IRB's Continuing Review Determination

Under 21 CFR 56.109(e), the IRB must "notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing."

After an IRB completes its continuing review, the IRB must provide written notification informing the investigator of the IRB's determination (e.g., approval, approval with modification(s) to secure approval, disapproval; 21 CFR 56.109(e)). For studies that are approved to continue, FDA recommends that the notification clearly state the date when approval is effective, the period of time for which the study is approved, and the next continuing review date.

When approving research with conditions at the time of continuing review, the IRB's notification should state 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. (Note that FDA would not consider such a suspension of subject enrollment at the time of continuing review to be a suspension of IRB approval that needs to be reported to appropriate institutional officials, the head (or designee) of the agency conducting or supporting the research, or FDA under 21 CFR 56.113.)

FDA recommends that IRBs notify the sponsor of any decision to disapprove the research and the reason(s) for the disapproval determination although they are not generally required to do

[22] See 21 CFR 312.53(c)(1)(vii); 312.60; 312.66; 812.36(c)(viii), 812.100, 812.110(b), 812.40, and 812.43(c)(4)(i).

so.[23] FDA encourages sponsors, clinical investigators, and IRBs to communicate with one another to protect the rights and welfare of study subjects.

H. Lapse, Suspension, or Termination of IRB Approval of Research

1. Lapse of IRB Approval

As discussed previously, the agency recommends that the IRB and the investigator plan ahead to ensure that continuing review and re-approval of research occurs prior to the end of the approval period specified by the IRB. FDA further recommends that the IRB's written procedures provide for sufficient advance notice to the investigator to ensure that the requirements for continuing review are met by the date on which approval would expire.

FDA regulations at 21 CFR part 56 make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. When continuing review of the research does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research by the expiration date of IRB approval. In such circumstances, all research activities involving human subjects must stop. Enrollment of new subjects cannot occur after the expiration of IRB approval.[24]

FDA expects that IRB procedures will be followed by investigators such that lapses of IRB approval will be a rare occurrence. However, temporarily continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects (e.g., investigational chemotherapy regimen in an oncology trial), or when withholding those interventions poses increased risk to the subjects.[25] If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research protocol, data collection (especially safety information) should also continue for such subjects (e.g., implantable device requiring long-term follow-up).

If the investigator is initially determining whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired, the investigator should consult the treating physician (if the investigator is not the treating physician). This determination may be made for all enrolled subjects as a group or for individual subjects. In all

[23]For studies involving an exception from informed consent for emergency research conducted under 21 CFR 50.24, an IRB must notify both the clinical investigator and the sponsor in writing of the IRB's determination that it cannot approve a study (21 CFR 50.24(e) and 56.109(e)).

[24] See, for example, 21 CFR 56.103(a) (studies that must meet requirements for prior submission in parts 312, 812, and 813 "shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part"); 21 CFR 812.110 (a) (investigator shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval); 21 CFR 312.66 (requiring investigators to assure that study is subject to continuing review by an IRB meeting the requirements of part 56).

[25] See 21 CFR 56.102(g).

cases, the investigator should verify that the IRB agrees with this determination as soon as possible.

We recommend that IRB procedures address how the investigator's determinations will be reviewed. FDA recommends that the procedures cover whether the IRB's review may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. In addition, the procedures should address whether the investigator's determination applies to one or more individuals or all enrolled subjects, timeframes, etc.

When IRB approval of ongoing research lapses and the investigator wants to continue the study, the IRB should complete continuing review for the study as soon as possible. Investigators may resume the study once continuing review and approval by the IRB has occurred. The IRB should document why the lapse occurred (e.g., insufficient number of IRB meetings to accommodate all continuing reviews, investigator failure to respond to a reminder notice of the anniversary date of approval, investigator failure to provide information to allow the IRB to conduct continuing review) and identify the steps taken to prevent any future lapses (e.g., modification of written procedures, adding more IRB meetings).

When IRB approval of an ongoing study lapses and the IRB subsequently re-approves the research, the IRB may approve the study for one year and establish a new anniversary date for the expiration date of subsequent approval periods. The IRB may also re-approve the research for a period of less than 1 year, either to retain the original anniversary date on which prior approval periods expired or to address study risks, in which case, a new date for continuing review is likely.

The lapse of IRB approval due to a failure to complete continuing review and obtain reapproval prior to expiration of the prior approval does not automatically constitute a suspension or termination of IRB approval, for reporting purposes under 21 CFR 56.113.[26] However, the failure to meet continuing review obligations may be grounds for suspension or termination under 21 CFR 56.113 (described below), in particular where the lapse of approval is not the first to occur in a study. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to FDA any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations, and any suspension or

[26] Conducting a study subject to IRB oversight during a period of lapsed approval, however, is a violation of an investigator's duties under FDA regulations. See 21 CFR 312.60 (investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations); 312.66 (requiring investigators to assure that study is subject to continuing review by an IRB meeting the requirements of part 56); 21 CFR 812.100 (investigators must ensure that study is conducted in accordance with applicable FDA regulations and conditions of IRB approval); 812.110(a) (investigator shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval); 21 CFR 56.103(a) (studies that must meet requirements for prior submission in parts 312, 812, and 813 "shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part").

termination of IRB approval (21 CFR 56.108(b)(2) and (3), and 56.113). FDA will evaluate such reports and may inspect the site, investigator, or IRB, as appropriate, to assess compliance with FDA's human subject protection regulations.

FDA also recommends that the IRB notify the sponsor of any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations, and any suspension or termination of IRB approval. Among the general responsibilities of sponsors is the assurance of proper monitoring of the investigation (21 CFR 312.50 and 21 CFR 812.40) and the selection of qualified investigators (21 CFR 312.53(a) and 21 CFR 812.43(a)). Informing sponsors of investigator non-compliance or IRB suspension or termination of the study allows the sponsor the opportunity to address these concerns. For example, the sponsor could work with the investigator to transfer subjects to another site in the local area, find a replacement investigator at the current site, or ensure that the study is terminated in an orderly manner.

2. Suspension or Termination of IRB Approval

The IRB has the authority to suspend or terminate approval of clinical investigations:

- that are not conducted in accordance with the IRB's requirements (21 CFR 56.113); or
- that are associated with unexpected serious harm to subjects (21 CFR 56.113).

Suspension of approval may be appropriate when a significant issue is first identified and while the IRB investigates the matter. For example, if there is an allegation of investigator misconduct or a safety issue that needs further investigation and evaluation, the IRB may decide to suspend the study until the matter is resolved. In addition, the IRB may determine whether it is appropriate to notify subjects, and if so, when, given that complete information may not be available when the IRB first becomes aware of the issue.

For multi-site studies in which a local IRB is responsible for review of research at a given site, the local IRB's decision to suspend or terminate its approval of the research only applies to the conduct of the research project at the site under its review. On the other hand, if many or all sites engaged in a multi-site study rely upon a central IRB for review of the research, the central IRB could suspend or terminate its approval of the research either at one site because of a problem regarding the conduct of the research at that site, or at all sites under its review because of a study-wide problem. If an IRB (whose authority is only over a single site) believes the problem it found may be present at other sites, the IRB should inform FDA of its concern in the suspension or termination notification.

Any suspension or termination of IRB approval must include the reasons for the IRB's actions and be promptly reported to the clinical investigator, institutional officials, and the FDA (21 CFR 56.113). IRBs must follow written procedures for ensuring such reporting (21 CFR 56.108(b)(3)).

When reporting suspensions or terminations of IRB approval to FDA, IRBs should include:

- the name of the drug, biologic, or device;

- the IND number; or the IDE number/non-significant risk (NSR) status of the device;
- the full name of the research protocol;
- the name(s) and address(es) of the clinical investigator(s);
- the reason(s) for the suspension or termination; and
- information about the IRB's investigation and action plan to prevent/address future non-compliance.

IRBs that have concerns about suspension or termination of approval of studies may contact FDA at any time to discuss these issues.[27]

When a study is suspended or terminated by the IRB, the IRB should consider the need to inform current or previously enrolled study subjects, as appropriate, about the action. In addition, an IRB should have established procedures to ensure that the rights and welfare of currently enrolled subjects are protected, subjects are not put at risk, and subjects receive appropriate care, if indicated, should the IRB (a) suspend or terminate its approval during the period for which IRB approval had already been given, or (b) disapprove a study at the time of continuing review. For example, the IRB, in consultation with the investigator and the subjects' treating physicians (if different from the investigator), may need to determine whether it is in the best interests of currently enrolled subjects to (a) continue receiving the interventions that were being administered to subjects under the study at the present site, (b) be transferred to another study-site so that participation of the subjects in the study may continue, or (c) be transitioned to medical management outside of the research context. Continuation of subjects on the test article may be appropriate, for example, when the test article holds out the prospect of direct benefit to the study subjects or when withholding the test article poses increased risk to study subjects. If the IRB decides that enrolled subjects should continue to receive the test article, it should also ensure that data collection (especially safety information) continues for such subjects. If follow-up of currently enrolled subjects is necessary to ensure their rights, safety or welfare, the IRB should ensure that the investigators inform the subjects, and report any unanticipated problems to the IRB, the sponsor, and the FDA (see 21 CFR 56.108(b)).

[27] See http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134493.htm for FDA points of contact to which IRB suspensions or terminations may be reported.

Appendix

CATEGORIES OF RESEARCH THAT MAY BE REVIEWED BY THE INSTITUTIONAL REVIEW BOARD (IRB) THROUGH AN EXPEDITED REVIEW PROCEDURE[\1\]

[Federal Register: November 9, 1998 (Volume 63, Number 216)] [Notices] [Page 60353-60356][*]

The list that is referenced in Sec. 56.110(a) was originally published in the Federal Register of January 27, 1981 (46 FR 8980), as a notice of a list of research activities that could be reviewed by the IRB through the expedited review procedures set forth in the FDA's regulations. OPRR has a separate codification that references the Expedited Review List for matters under the Department of Health and Human Services' (HHS) jurisdiction (45 CFR part 46). The HHS list was published in the Federal Register on January 26, 1981 (46 FR 8392). The FDA and HHS lists published in 1981 differ slightly, in that item nine on the HHS list, concerning research on individual or group behavior, pertains only to 45 CFR 46.110. Because behavioral research is not specifically regulated by FDA, that category was not included in the list published by FDA.

Applicability

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. (B) The categories in this list apply regardless of the age of subjects, except as noted. (C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. (D) The expedited review procedure may not be used for classified research involving human subjects. (E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB. (F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

[\1\] An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

[*] The list may be viewed online via GPO Access at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed.pdf

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required;

(Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children,[\2\] considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylatic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance

[\2\] Children are defined in the HHS regulations as ``persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows: (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) Where no subjects have been enrolled and no additional risks have been identified; or (c) Where the remaining research activities are limited to data analysis.

(9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through 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.

Guidance for Clinical Investigators, Sponsors, and IRBs

Adverse Event Reporting to IRBs — Improving Human Subject Protection

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner (OC)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)

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Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Sponsors, and IRBs[1] Adverse Event Reporting to IRBs — Improving Human Subject Protection

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.

I. INTRODUCTION

This guidance is intended to assist the research community in interpreting requirements for submitting reports of *unanticipated problems*, including certain adverse events reports, to the institutional review board (IRB) under Title 21 of the Code of Federal Regulations (21 CFR) part 56 (Institutional Review Boards), part 312 (Investigational New Drug Application), and part 812 (Investigational Device Exemptions). Specifically, the guidance provides recommendations for sponsors and investigators conducting investigational new drug (IND) trials to help them differentiate between those adverse events that are unanticipated problems that must be reported to an IRB and those that are not. The guidance also makes suggestions about how to make communicating adverse events information to IRBs more efficient.

FDA developed this guidance in response to concerns raised by the IRB community, including concerns raised at a March 2005 public hearing,[2] that increasingly large volumes of individual adverse event reports submitted to IRBs—often lacking in context and detail—are inhibiting, rather than enhancing, the ability of IRBs to protect human subjects.

FDA regulations use different terms when referring to an *adverse event*. For example, *adverse effect* is used in 21 CFR 312.64; *adverse experience* is used in § 312.32; and *unanticipated problems* is used in § 312.66. For the purposes of this guidance, the term *adverse event* is used, except when quoting specific regulations. For device studies, part 812 uses the term *unanticipated adverse device effect*, which is defined in 21 CFR 812.3(s).

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

[1] This guidance has been prepared by the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Good Clinical Practice Program (GCPP) at the Food and Drug Administration.

[2] *Federal Register,* "Reporting of Adverse Events to Institutional Review Boards; Public Hearing," (70 FR 6693, March 21, 2005).

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

FDA regulates clinical studies authorized under sections 505(i) (drugs and biologics) and 520(g) (devices) of the Federal Food, Drug, and Cosmetic Act. All such clinical studies must be reviewed and approved by an IRB before the study is initiated, in accordance with the requirements of 21 CFR part 50 (Protection of Human Subjects), part 56 (Institutional Review Boards), and either part 312 (Investigational New Drug Application) or part 812 (Investigational Device Exemptions) (see §§ 50.1, 56.101, 312.23(a)(1)(iv), 312.40(a), 812.2(b)(1)(ii), 812.2(c) and 812.62(a)).[3] After the initial review and approval of a clinical study, an IRB must conduct continuing review of the study at intervals appropriate to the degree of risk presented by the study, but at least annually (§ 56.109(f)). The primary purpose of both initial and continuing review of the study is "to assure the protection of the rights and welfare of the human subjects" (§ 56.102(g)). To fulfill its obligations during the conduct of a clinical study, an IRB must have, among other things, information concerning unanticipated problems involving risk to human subjects in the study, including adverse events (AEs) that are considered unanticipated problems (§§ 56.108(a)(3), (4), (b)).[4]

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, information about adverse events[5] must be communicated among investigators, sponsors, and IRBs as follows:

- Investigators are required to report promptly "to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (§ 312.64(b)).
- Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report of "any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)). And, more generally, sponsors are required to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use" (§ 312.55(b)).

[3] As described below, there are some differences between the requirements for investigational new drug and investigational device exemption studies, as they concern obligations to report to a reviewing IRB.
[4] Unanticipated problems may be adverse events or other types of problems, i.e., adverse events are a subset of unanticipated problems.
[5] The IND regulations use the term *adverse effect* (§ 312.64) and *adverse experience* (§ 312.32). These terms are interchangeable with *adverse event*.

- Investigators are required to report promptly "to the IRB… all *unanticipated problems* involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

A critical question for studies conducted under part 312 is what adverse events ***should*** be considered *unanticipated problems* that merit reporting to an IRB. In the years since the IRB and IND regulations issued, changes in the conduct of clinical trials (e.g., increased use of multi-center studies, international trials) have complicated the reporting pathways for adverse event information described in the regulations. In particular, the practice of local investigators reporting individual, unanalyzed events to IRBs, including reports of events from other study sites that the investigator receives from the sponsor of a multi-center study—often with limited information and no explanation of how the event represents an unanticipated problem—has led to the submission of large numbers of reports to IRBs that are uninformative. IRBs have expressed concern that the way in which investigators and sponsors of IND studies typically interpret the regulatory requirement to inform IRBs of all "unanticipated problems" does not yield information about adverse events that is useful to IRBs and thus hinders their ability to ensure the protection of human subjects. This guidance is intended to help differentiate those adverse events that should be considered unanticipated problems (and thus reported to the IRB) from those that should not, thereby helping to ease the burden on IRBs and make the adverse events information they receive more informative and useful.

III. REPORTING AEs TO IRBs IN CLINICAL TRIALS OF DRUG AND BIOLOGICAL PRODUCTS CONDUCTED UNDER IND REGULATIONS

A. How to Determine If an AE is an Unanticipated Problem that Needs to Be Reported

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

Many types of AEs generally require an evaluation of their relevance and significance to the study, including an aggregate analysis of other occurrences of the same (or similar) event, before they can be determined to be an unanticipated problem involving risk to human subjects. For example, an aggregate analysis of a series of AEs that are commonly associated with the underlying disease process that the study intervention is intended to treat (e.g., deaths in a cancer trial), or that are otherwise common in the study population independent of drug exposure (e.g., cardiovascular events in an elderly population) may reveal that the event rate is higher in the drug treatment group compared to the control arm. In this case, the AE would be considered an unanticipated problem. In the absence of such a finding, the event is uninterpretable.

The major exceptions to the general rule that an isolated event is not informative are serious AEs that are uncommon and strongly associated with drug exposure, such as angioedema, agranulocytosis, anaphylaxis, hepatic injury, or Stevens Johnson syndrome. In most cases, a single, unexpected occurrence of this type of event would be considered an unanticipated problem involving risk to human subjects and, thus, must be reported to the IRB. Similarly, one or a small number of serious events that are not commonly associated with drug exposure, but are otherwise uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy) should be considered an unanticipated problem involving risk to human subjects.

Because they have been previously observed with a drug, the AEs listed in the investigator's brochure would, by definition,[6] not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

Therefore, FDA recommends that there be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. In summary, FDA believes that only the following AEs should be considered as *unanticipated problems* that must be reported to the IRB.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an

[6] An unexpected adverse drug experience is defined as "[a]ny adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. *Unexpected*, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure), rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product." (21 CFR 312.32(a))

unanticipated problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.

- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). We recommend that a discussion of the divergence from the expected rate accompany the report.
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

B. How to Report Unanticipated Problems to IRBs

In a multicenter study, it is clear that individual investigators must rely on the sponsor to provide them information about AEs occurring at other study sites. It is also clear that the sponsor receives AE information from all study sites and typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and—when the determination relies on information from multiple study sites or other information not readily accessible to the individual investigators (e.g., a sponsor's preclinical data that supports the determination)—to make a determination about whether an AE is an unanticipated problem. Furthermore, the regulations require the sponsor of an IND to promptly review all information relevant to the safety of the drug and to consider the significance of the report within the context of other reports (§ 312.32)[7]

The regulations state that for studies conducted under 21 CFR part 312, investigators must report all "unanticipated problems" to the IRB (§§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1)). However, as discussed above, we recognize that for multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both *unanticipated* and a *problem* for the study.

Accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, because the investigator, sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB,[8] and because the investigator was copied on the report from the

[7] Section 312.32(c)(1)(ii) requires a sponsor preparing an IND safety report to, among other things, "analyze the significance of the adverse experience in light of previous, similar reports." Section 312.32(b) requires the sponsor to "promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source . . . ."

[8] Note that such an agreement would be required to be incorporated into the IRB's written procedures (21 CFR 56.108(b)(1), 56.115(a)(6)).

sponsor to the IRB, FDA intends to exercise its enforcement discretion and would not expect an investigator to provide the IRB with a duplicate copy of the report received from the sponsor.

IV. REPORTING AEs TO IRBs IN CLINICAL TRIALS OF DEVICES UNDER THE IDE REGULATIONS

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

V. CONCLUSION

The receipt of a large volume of individual AE reports without analysis of their significance to a clinical trial rarely supports an IRB's efforts to ensure human subject protection. Sponsors can assess the implications and significance of AE reports promptly and are required to report serious, unexpected events associated with the use of a drug or device, including analyses of such events, to investigators and to FDA. In addition, sponsors are required to report analyses of unexpected adverse device experiences to IRBs. FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful AE information. The ultimate goal is to provide more meaningful information to IRBs, particularly when sponsor analysis (including an analysis of the significance of the adverse event, with a discussion of previous similar events where appropriate) is made available to IRBs.

http://www.hhs.gov/ohrp/policy/advevntguid.html#Q3

Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events

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 at 240-453-6900 or 866-447-4777.

Date: January 15, 2007

Scope: This document applies to non-exempt human subjects research conducted or supported by HHS. It provides guidance on HHS regulations for the protection of human research subjects at 45 CFR part 46 related to the review and reporting of (a) unanticipated problems involving risks to subjects or others (**hereinafter referred to as unanticipated problems**); and (b) adverse events. In particular, this guidance clarifies that only a small subset of adverse events occurring in human subjects participating in research are unanticipated problems that must be reported under 45 CFR part 46. The guidance is intended to help ensure that the review and reporting of unanticipated problems and adverse events occur in a timely, meaningful way so that human subjects can be better protected from avoidable harms while reducing unnecessary burden.

The guidance addresses the following topics:

Appendices

NOTE: For some HHS-conducted or -supported research, the Food and Drug Administration (FDA) and the HHS agency conducting or supporting the research (e.g., the National Institutes of Health [NIH]) may have separate regulatory and policy requirements regarding the reporting of unanticipated problems and adverse events. Anyone needing guidance on the reporting requirements of FDA or other HHS agencies should contact these agencies directly. Furthermore, investigators and IRBs should be cognizant of any applicable state and local laws and regulations related to unanticipated problems and adverse events experienced by research subjects, as well as foreign requirements for research conducted outside the United States. OHRP recommends that investigators and IRBs consult with their legal advisors for guidance regarding pertinent state, local, and international laws and regulations.

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

Regulatory Background:

HHS regulations for the protection of human subjects (45 CFR part 46) contain five specific requirements relevant to the review and reporting of unanticipated problems and adverse events:

1. Institutions engaged in human subjects research conducted or supported by HHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)).

2. For research covered by an assurance approved for federalwide use by OHRP, HHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.

3. In order to approve research conducted or supported by HHS, the IRB must determine, among other things, that:

   a. 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 subject for diagnostic or treatment purposes (45 CFR 46.111(a)(1)).

   b. Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).

   c. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)).

4. An IRB must conduct continuing review of research conducted or supported by HHS at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research (45 CFR 46.109(e)).

5. An IRB must have authority to suspend or terminate approval of research conducted or supported by HHS that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval must include a statement of the reasons for the IRB's action and must be reported promptly to the investigator, appropriate institutional officials, and any supporting department or agency head (45 CFR 46.113).

Guidance:

I. What are *unanticipated problems*?

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks; and
- provision of additional information about newly recognized risks to previously enrolled subjects.

As discussed in the sections II and III below, only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem.

Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs. Appendix B provides examples of unanticipated problems that do not involve adverse events but must be reported under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

II. What are *adverse events*?

The HHS regulations at 45 CFR part 46 do not define or use the term *adverse event*, nor is there a common definition of this term across government and non-government entities. In this guidance document, the term *adverse event* in general is used very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

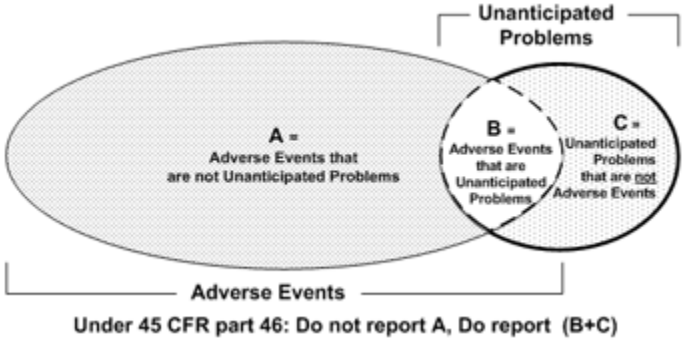
In the context of multicenter clinical trials, adverse events can be characterized as either *internal adverse events* or *external adverse events*. From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution, whereas *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

In the case of an *internal adverse event* at a particular institution, an investigator at that institution typically becomes aware of the event directly from the subject, another collaborating investigator at the same institution, or the subject's healthcare provider. In the case of *external adverse events*, the investigators at all participating institutions learn of such events via reports that are distributed by the sponsor or coordinating center of the multicenter clinical trials. At many institutions, reports of external adverse events represent the majority of adverse event reports currently being submitted by investigators to IRBs.

III. How do you determine which *adverse events* are *unanticipated problems*?

In OHRP's experience, most IRB members, investigators, and institutional officials understand the scope and meaning of the term *adverse event* in the research context, but lack a clear understanding of OHRP's expectations for what, when, and to whom adverse events need to be reported as unanticipated problems, given the requirements of the HHS regulations at 45 CFR part 46.

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



Under 45 CFR part 46: Do not report A, Do report (B+C)

The diagram illustrates three key points:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
    - A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

The key question regarding a particular adverse event is whether it meets the three criteria described in section I and therefore represents an unanticipated problem. To determine

whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the adverse event unexpected?
- Is the adverse event related or possibly related to participation in the research?
- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is *yes,* then the adverse event is an unanticipated problem and must be reported to appropriate entities under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5). The next three sub-sections discuss the assessment of these three questions.

A. Assessing whether an adverse event is *unexpected*

In this guidance document, OHRP defines *unexpected adverse event* as follows:

Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

(Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

Examples of *unexpected* adverse events under this definition include the following:

- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information did not identify liver disease as a potential adverse event;
- Hodgkin's disease (HD) occurring in a subject without predisposing risk factors for HD would be an unexpected adverse event (by virtue of its unexpected nature) if the protocol-related documents and other relevant sources of information only referred to acute myelogenous leukemia as a potential adverse event; and
- liver failure due to diffuse hepatic necrosis occurring in a subject without any underlying liver disease would be an unexpected adverse event (by virtue of its unexpected greater severity) if the protocol-related documents and other relevant sources of information only referred to elevated hepatic enzymes or hepatitis as potential adverse events related to the procedures involved in the research.

In comparison, prolonged severe neutropenia and opportunistic infections occurring in subjects administered an experimental chemotherapy regimen as part of an oncology clinical trial would be examples of *expected* adverse events if the protocol-related documents described prolonged severe neutropenia and opportunistic infections as common risks for all subjects.

OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected. OHRP notes that for many studies, determining whether a particular adverse event is unexpected by virtue of an unexpectedly higher frequency can only be done through an analysis of appropriate data on all subjects enrolled in the research.

In OHRP's experience the vast majority of adverse events occurring in the context of research are *expected* in light of (1) the known toxicities and side effects of the research procedures; (2) the expected natural progression of subjects' underlying diseases, disorders, and conditions; and (3) subjects' predisposing risk factor profiles for the adverse events. Thus, most individual adverse events do not meet the first criterion for an unanticipated problem and do not need to be reported under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5) (see examples (1)-(4) in Appendix C).

B. Assessing whether an adverse event is *related or possibly related to participation in research*

Adverse events may be caused by one or more of the following:

1. the procedures involved in the research;

2. an underlying disease, disorder, or condition of the subject; or

3. other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by (2) or (3) would be considered unrelated to participation in the research.

For example, for subjects with cancer participating in oncology clinical trials testing chemotherapy drugs, neutropenia and anemia are common adverse events related to participation in the research. Likewise, if a subject with cancer and diabetes mellitus participates in an oncology clinical trial testing an investigational chemotherapy agent and experiences a severe hypoglycemia reaction that is determined to be caused by an interaction between the subject's diabetes medication and the investigational chemotherapy agent, such a hypoglycemic reaction would be another example of an adverse event related to participation in the research.

In contrast, for subjects with cancer enrolled in a non-interventional, observational research registry study designed to collect longitudinal morbidity and mortality outcome data on the subjects, the death of a subject from progression of the cancer would be an adverse event that is related to the subject's underlying disease and is unrelated to participation in the research. Finally, the death of a subject participating in the same cancer research registry study from being struck by a car while crossing the street would be an adverse event that is unrelated to both participation in the research and the subject's underlying disease.

Determinations about the relatedness of adverse events to participation in research commonly result in probability statements that fall along a continuum between definitely *related* to the research and definitely *unrelated* to participation in the research. OHRP considers *possibly related* to participation in the research to be an important threshold for determining whether a particular adverse event represents an unanticipated problem. In this guidance document, OHRP defines *possibly related* as follows:

There is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).

OHRP recognizes that it may be difficult to determine whether a particular adverse event is related or possibly related to participation in the research.

Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5) (see examples (5) and (6) in Appendix C).

C. Assessing whether an adverse event *suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized*

The first step in assessing whether an adverse event meets the third criterion for an unanticipated problem is to determine whether the adverse event is *serious*.

In this guidance document, OHRP defines *serious adverse event* as any adverse event that:

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);

3. results in inpatient hospitalization or prolongation of existing hospitalization;

4. results in a persistent or significant disability/incapacity;

5. results in a congenital anomaly/birth defect; or

6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

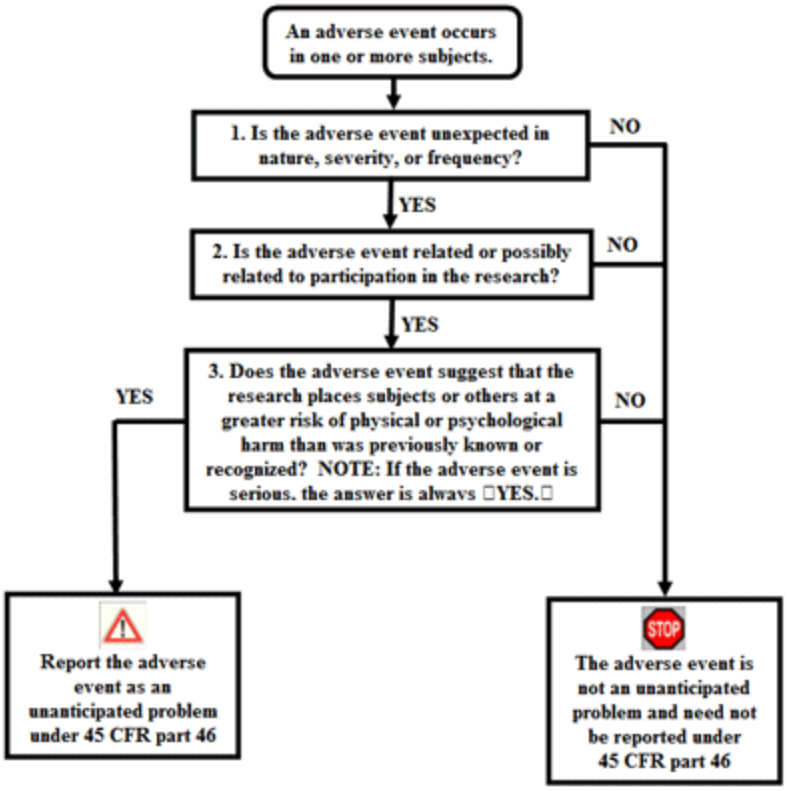
(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

OHRP considers adverse events that are unexpected, related or possibly related to participation in research, and *serious* to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects (see examples (1)-(4) in section Appendix D).

Furthermore, OHRP notes that IRBs have authority to suspend or terminate approval of research that, among other things, has been associated with unexpected serious harm to subjects (45 CFR 46.113). In order for IRBs to exercise this important authority in a timely manner, they must be informed promptly of those adverse events that are unexpected, related or possibly related to participation in the research, and serious (45 CFR 46.103(b)(5)).

However, other adverse events that are unexpected and related or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others (see examples (5) and (6) in Appendix D).

The flow chart below provides an algorithm for determining whether an adverse event represents an unanticipated problem that needs to be reported under HHS regulations at 45 CFR part 46.



IV. What are other important considerations regarding the reviewing and reporting of unanticipated problems and adverse events?

A. Reporting of *internal* adverse events by *investigators to IRBs*

For an internal adverse event, a local investigator typically becomes aware of the event directly from the subject, another collaborating local investigator, or the subject's healthcare provider.

Upon becoming aware of an internal adverse event, the investigator should assess whether the adverse event represents an unanticipated problem following the guidelines described in section III above. If the investigator determines that the adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)).

Regardless of whether the internal adverse event is determined to be an unanticipated problem, the investigator also must ensure that the adverse event is reported to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) *if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy*.

If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB (45 CFR 46.103(b)(5)).

B. Reporting of *external* adverse events by *investigators to IRBs*

Investigators and IRBs at many institutions routinely receive a large volume of reports of external adverse events experienced by subjects enrolled in multicenter clinical trials. These external adverse event reports frequently represent the majority of adverse event reports submitted by investigators to IRBs. OHRP notes that reports of individual external adverse

events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

OHRP advises that it is neither useful nor necessary under the HHS regulations at 45 CFR part 46 for reports of individual adverse events occurring in subjects enrolled in multicenter studies to be distributed routinely to investigators or IRBs at all institutions conducting the research. Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem. In general, the investigators and IRBs at all these institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46. Typically, such reports to the IRBs are submitted by investigators. OHRP recommends that any distributed reports include: (1) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem; and (2) a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether it identifies the adverse event as being:

1. unexpected;

2. related or possibly related to participation in the research; and

3. serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only external adverse events that are identified in the report as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems under HHS regulations at 45 CFR 46.103(b)(5). OHRP expects that individual external adverse events rarely will meet these criteria for an unanticipated problem.

C. Reporting of *other unanticipated problems* (not related to adverse events) by *investigators to IRBs*

Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event; see Appendix B for examples) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria described in section I. If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)).

D. *Content of reports* of unanticipated problems submitted to IRBs

OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

1. appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;

2. a detailed description of the adverse event, incident, experience, or outcome;

3. an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem; and

(4) a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

E. *Changes to a multicenter research protocol* that are proposed by an investigator at one institution in response to an unanticipated problem

For multicenter research protocols, if a local investigator at one institution engaged in the research independently proposes changes to the protocol or informed consent document in response to an unanticipated problem, the investigator should consult with the study sponsor or coordinating center regarding the proposed changes because changes at one site could have significant implications for the entire research study.

F. IRB review and further reporting of unanticipated problems

Once reported to the IRB, further review and reporting of any unanticipated problems must proceed in accordance with the institution's written procedures for reporting unanticipated problems, as required by HHS regulations at 45 CRF 46.103(b)(5). The HHS regulations at 45 CFR part 46 do not specify requirements for how such unanticipated problems are reviewed by the IRB. Therefore, IRBs are free to implement a wide range of procedures for reviewing unanticipated problems, including review by the IRB chairperson or another IRB member, a subcommittee of the IRB, or the convened IRB, among others. When reviewing a report of an unanticipated problem, the IRB should consider whether the affected research protocol still satisfies the requirements for IRB approval under HHS regulations at 45 CFR 46.111. In particular, the IRB should consider whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.

When reviewing a particular incident, experience, or outcome reported as an unanticipated problem by the investigator, the IRB may determine that the incident, experience, or outcome does not meet all three criteria for an unanticipated problem. In such cases, further reporting to appropriate institutional officials, the department or agency head (or designee), and OHRP would not be required under HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

The IRB has authority, under HHS regulations at 45 CFR 46.109(a), to require, as a condition of continued approval by the IRB, submission of more detailed information by the investigator(s), the sponsor, the study coordinating center, or DSMB/DMC about any adverse event or unanticipated problem occurring in a research protocol.

Any proposed changes to a research study in response to an unanticipated problem must be reviewed and approved by the IRB before being implemented, except when necessary to eliminate apparent immediate hazards to subjects. If the changes are more than minor, the changes must be reviewed and approved by the convened IRB (45 CFR 46.103(b)(4) and 46.110(a)). OHRP recommends that for multicenter research protocols, if the IRB proposes changes to the protocol or informed consent documents/process in addition to those proposed by the study sponsor, coordinating center, or local investigator, the IRB should request in writing that the local investigator discuss the proposed modifications with the study sponsor or coordinating center and submit a response or necessary modifications for review by the IRB.

Institutions must have written procedures for reporting unanticipated problems to appropriate institutional officials (45 CFR 46.103(b)(5)). The regulations do not specify who the appropriate institutional officials are. Institutions may develop written procedures that specify different institutional officials as being appropriate for different types of unanticipated problems. For example, an institution could develop written procedures designating the IRB chairperson and members as the only appropriate institutional officials to whom *external* adverse events that are unanticipated problems are to be reported, and designating the Vice President for Research as an additional appropriate institutional official to whom *internal* adverse events that are unanticipated problems are to be reported by the IRB chairperson.

G. Reporting unanticipated problems to OHRP and supporting agency heads (or designees)

Unanticipated problems occurring in research covered by an OHRP-approved assurance also must be reported by the institution to the supporting HHS agency head (or designee) and OHRP (45 CFR 46.103(a)). Typically, the IRB chairperson or administrator, or another appropriate institutional official identified under the institution's written IRB procedures, is responsible for reporting unanticipated problems to the supporting HHS agency head (or designee) and OHRP. For further information on reporting to OHRP, see the Guidance on Reporting Incidents to OHRP.

For multicenter research projects, only the institution at which the subject(s) experienced an adverse event determined to be an unanticipated problem (or the institution at which any other type of unanticipated problem occurred) must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.103(b)(5)). Alternatively, the central monitoring entity may be designated to submit reports of unanticipated problems to the supporting agency head (or designee) and OHRP.

V. What is the appropriate time frame for reporting unanticipated problems to the IRB, appropriate institutional officials, the department or agency head (or designee), and OHRP?

The HHS regulations at 46.103(b)(5) require written procedures for ensuring *prompt* reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm.

The regulations do not define *prompt*. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, OHRP recommends the following guidelines in order to satisfy the requirement for *prompt* reporting:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.

2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

3. All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

OHRP notes that, in some cases, the requirements for prompt reporting may be met by submitting a preliminary report to the IRB, appropriate institutional officials, the supporting HHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other subjects.

VI. What should the IRB consider at the time of initial review with respect to adverse events?

Before research is approved and the first subject enrolled, the investigator(s) and the IRB should give appropriate consideration to the spectrum of adverse events that might occur in subjects. In particular, in order to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111(a)(1), (2), and (6), the IRB needs to receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the adverse events that may

be caused by the procedures involved in the research. The investigator also should describe how the risks of the research will be minimized.

In addition, depending upon the risks of the research and the likelihood that the research could involve risks to subjects that are unforeseeable, the IRB must ensure, if appropriate, that the research includes adequate provisions for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6)). Such provisions typically would include monitoring, among other things, adverse events and unanticipated problems that may occur in subjects enrolled in the research. The HHS regulations at 45 CFR part 46 do not require that the IRB conduct such monitoring, and OHRP believes that, in general, the IRB is *not* the appropriate entity to monitor research.

OHRP notes that adequate monitoring provisions for research, if deemed appropriate by the IRB, might include one or more of the following elements, among others:

1. The type of data or events that are to be captured under the monitoring provisions.

2. The entity responsible for monitoring the data collected, including data related to unanticipated problems and adverse events, and their respective roles (e.g., the investigators, the research sponsor, a coordinating or statistical center, an independent medical monitor, a DSMB/DMC, and/or some other entity). (OHRP notes that the IRB has authority to observe or have a third party observe the research (45 CFR 46.109(e).)

3. The time frames for reporting adverse events and unanticipated problems to the monitoring entity.

4. The frequency of assessments of data or events captured by the monitoring provisions.

5. Definition of specific triggers or stopping rules that will dictate when some action is required.

6. As appropriate, procedures for communicating to the IRB(s), the study sponsor, the investigator(s), and other appropriate officials the outcome of the reviews by the monitoring entity.

The monitoring provisions should be tailored to the expected risks of the research; the type of subject population being studied; and the nature, size (in terms of projected subject enrollment and the number of institutions enrolling subjects), and complexity of the research protocol.

For example, for a multicenter clinical trial involving a high level of risk to subjects, frequent monitoring by a DSMB/DMC may be appropriate, whereas for research involving no more than minimal risk to subjects, it may be appropriate to not include any monitoring provisions.

VII. What should the IRB consider at the time of continuing review with respect to unanticipated problems and adverse events?

For non-exempt research conducted or supported by HHS, the IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)). At the time of continuing review, the IRB should ensure that the criteria for IRB approval under HHS regulations at 45 CFR 46.111 continue to be satisfied. In particular, the IRB needs to determine whether any new information has emerged – either from the research itself or from other sources – that could alter the IRB's previous determinations, particularly with respect to risk to subjects. Information regarding any unanticipated problems that have occurred since the previous IRB review in most cases will be pertinent to the IRB's determinations at the time of continuing review.

It may also be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring study data to ensure safety of subjects have been implemented and are working as intended (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

OHRP recommends that, among other things, a summary of any unanticipated problems and available information regarding adverse events and any recent literature that may be relevant to the research be included in continuing review reports submitted to the IRB by investigators. OHRP notes that the amount of detail provided in such a summary will vary depending on the type of research being conducted. In many cases, such a summary could be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

OHRP recognizes that local investigators participating in multicenter clinical trials usually are unable to prepare a meaningful summary of adverse events for their IRBs because study-wide information regarding adverse events is not readily available to them. In such circumstances, when the clinical trial is subject to oversight by a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC), OHRP recommends that at the time of continuing review local investigators submit to their IRBs a current report from the monitoring entity. OHRP further recommends that such reports include the following:

1. a statement indicating what information (e.g., study-wide adverse events, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;

2. the date of the review; and

3. the monitoring entity's assessment of the information reviewed.

For additional details about OHRP's guidance on continuing review, see http://www.hhs.gov/ohrp/policy/contrev0107.html.

VIII. What should written IRB procedures include with respect to reporting unanticipated problems?

Written IRB procedures should provide a step-by-step description with key operational details for complying with the reporting requirements described in HHS regulations at 45 CFR 46.103(b)(5). Important operational details for the required reporting procedures should include:

1. The type of information that is to be included in reports of unanticipated problems.

2. A description of which office(s) or individual(s) is responsible for promptly reporting unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency heads (or designees), and OHRP.

3. A description of the required time frame for accomplishing the reporting requirements for unanticipated problems.

4. The range of the IRB's possible actions in response to reports of unanticipated problems.

OHRP notes that many institutions have written IRB procedures for reporting adverse events, but do not address specifically the reporting requirements for unanticipated problems. Such institutions should expand their written IRB procedures to include reporting requirements for unanticipated problems.

Appendix A

Glossary for Key Terms

Adverse event: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from

the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug* in FDA regulations at 21 CFR 312.32(a)).

Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);

3. requires inpatient hospitalization or prolongation of existing hospitalization;

4. results in a persistent or significant disability/incapacity;

5. results in a congenital anomaly/birth defect; or

6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Unanticipated problem involving risks to subjects or others: Any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. related or possibly related to a subject's participation in the research; and

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Unexpected adverse event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current

IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

(Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

Appendix B

Examples of Unanticipated Problems that Do Not Involve Adverse Events and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

1. An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the investigators did not anticipate the theft); (b) related to participation in the research; and (c) placed the subjects at a greater risk of psychological and social harm from the breach in confidentiality of the study data than was previously known or recognized.

2. As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is 10-times higher than the dose dictated by the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported to the IRB, appropriate institutional officials, and OHRP because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subject at a greater risk of physical harm than was previously known or recognized.

3. Subjects with cancer are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus. This constitutes an unanticipated problem that must be reported because the incident was (a) unexpected; (b) related to participation in the research; and (c) placed subjects and others at a greater risk of physical harm than was previously known or recognized.

The events described in the above examples were unexpected in nature, related to participation in the research, and resulted in new circumstances that increased the risk of harm to subjects. In all of these examples, the unanticipated problems warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the IRB, appropriate institutional officials, the supporting agency head and OHRP in accordance with HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

Appendix C

Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to be Reported under the HHS Regulations at 45 CFR Part 46

1. A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document. The investigators conclude that the subject's infection and death are directly related to the research interventions. A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection, and death are within the expected frequency. This example is not an unanticipated problem because the occurrence of severe infections and death – in terms of nature, severity, and frequency – was expected.

2. A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB-approved protocol and informed consent document for the study indicated that the there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers – in terms of nature, severity, and frequency – was expected.

3. A subject is enrolled in a phase 3, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The IRB-approved protocol and informed consent document for the study indicated that there was a 5-10% chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject's stroke resulted from the research intervention. This example is not an unanticipated problem because the occurrence of stroke was expected and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level.

4. An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.

5. A subject with advanced renal cell carcinoma is enrolled in a study evaluating the effects of hypnosis for the management of chronic pain in cancer patients. During the subject's

initial hypnosis session in the pain clinic, the subject suddenly develops acute chest pain and shortness of breath, followed by loss of consciousness. The subject suffers a cardiac arrest and dies. An autopsy reveals that the patient died from a massive pulmonary embolus, presumed related to the underlying renal cell carcinoma. The investigator concludes that the subject's death is unrelated to participation in the research. This example is not an unanticipated problem because the subject's pulmonary embolus and death were attributed to causes other than the research interventions.

6. An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting. This example is not an unanticipated problem because the death of the subject is not related to participation in the research, but is most likely related to the infant's underlying medical condition.

NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are not unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research. In addition, the assessment of the relationship between the expected and actual frequency of a particular adverse event must take into account a number of factors including the uncertainty of the expected frequency estimates, the number and type of individuals enrolled in the study, and the number of subjects who have experienced the adverse event.

Appendix D

Examples of Adverse Events that Represent Unanticipated Problems and Need to be Reported Under the HHS Regulations at 45 CFR Part 46

1. A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo-controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the subject's acute renal failure was (a) unexpected in nature, (b) related to participation in the research, and (c) serious.

2. A subject with seizures enrolls in a randomized, phase 3 clinical trial comparing a new investigational anti-seizure agent to a standard, FDA-approved anti-seizure medication. The subject is randomized to the group receiving the investigational agent. One month after enrollment, the subject is hospitalized with severe fatigue and on further evaluation is noted to have severe anemia (hematocrit decreased from 45% pre-randomization to 20%). Further hematologic evaluation suggests an immune-mediated hemolytic anemia. The known risk profile of the investigational agent does not include anemia, and the IRB-approved protocol and informed consent document for the study do not identify anemia as a risk of the research. The investigators determine that the hemolytic anemia is possibly due to the investigational agent. This is an example of an unanticipated problem that must be reported because the hematologic toxicity was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) serious.

3. The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk

profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an unanticipated problem that must be reported because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was (a) unexpected in severity; (b) possibly related to participation in the research; and (c) serious.

4. Subjects with coronary artery disease presenting with unstable angina are enrolled in a multicenter clinical trial evaluating the safety and efficacy of an investigational vascular stent. Based on prior studies in animals and humans, the investigators anticipate that up to 5% of subjects receiving the investigational stent will require emergency coronary artery bypass graft (CABG) surgery because of acute blockage of the stent that is unresponsive to non-surgical interventions. The risk of needing emergency CABG surgery is described in the IRB-approved protocol and informed consent document. After the first 20 subjects are enrolled in the study, a DSMB conducts an interim analysis, as required by the IRB-approved protocol, and notes that 10 subjects have needed to undergo emergency CABG surgery soon after placement of the investigational stent. The DSMB monitoring the clinical trial concludes that the rate at which subjects have needed to undergo CABG greatly exceeds the expected rate and communicates this information to the investigators. This is an example of an unanticipated problem that must be reported because (a) the frequency at which subjects have needed to undergo emergency CABG surgery was significantly higher than the expected frequency; (b) these events were related to participation in the research; and (c) these events were serious.

5. Subjects with essential hypertension are enrolled in a phase 2, non-randomized clinical trial testing a new investigational antihypertensive drug. At the time the clinical trial is initiated, there is no documented evidence of gastroesophageal reflux disease (GERD) associated with the investigational drug, and the IRB-approved protocol and informed consent document do not describe GERD as a risk of the research. Three of the first ten subjects are noted by the investigator to have severe GERD symptoms that began within one week of starting the investigational drug and resolved a few days after the drug was discontinued. The investigator determines that the GERD symptoms were most likely caused by the investigational drug and warrant modification of the informed consent document to include a description of GERD as a risk of the research. This is an example of an adverse event that, although not serious, represents an unanticipated problem that must be reported because it was (a) unexpected in nature; (b) possibly related to participation in the research; and (c) suggested that the research placed subjects at a greater risk of physical harm than was previously known or recognized.

6. A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from certain survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected; (b) related to participation in the research; and (c) suggested that the research places subjects at a greater risk of psychological harm than was previously known or recognized.

In all of these examples, the adverse events warranted consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

NOTE: For purposes of illustration, the case examples provided above represent generally unambiguous examples of adverse events that are unanticipated problems. OHRP recognizes that it may be difficult to determine whether a particular adverse event is unexpected and whether it is related or possibly related to participation in the research.

FOR IRB USE ONLY
$STAMP_IRB
$STAMP_IRB_ID
$STAMP_APPRV_DT

[Information noted in Bold in the Informed Consent Template are instructions for the research team in completing sections of this document and should be removed or updated, as applicable, prior to submitting the project in HawkIRB for IRB review.]

INFORMED CONSENT DOCUMENT

Project Title: **$PROJECT_LONG_TITLE**

Principal Investigator: $PI_NAME

Research Team Contact: **[Insert the name and phone number of at least one research team member for subjects to contact with questions, concerns, or problems. This may be the PI of the study if no other research team member is appropriate.]**

#if($CHILDREN)**[Use the box below if your study involves teenagers who would assent by signing this form, along with their parent/legal guardian. Use the second person ("you") throughout the document – do not use "you/your child".]**

- If you are the parent/guardian of a child under 18 years old who is being invited to be in this study, the word "you" in this document refers to your child. You will be asked to read and sign this document to give permission for your child to participate.
- If you are a teenager reading this document because you are being invited to be in this study, the word "you" in this document refers to you. You will be asked to read and sign this document to indicate your willingness to participate.

#end

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you **[complete this sentence by describing why the person reading the consent is a possible subject for your project. For example, …have been diagnosed with lung cancer, …are a jogger, …are a healthy adult, etc.]**

The purpose of this research study is **[general description of the project – what is being investigated, what is the hypothesis, what knowledge or information is being sought and why]**

#if($INVESTIGATIONAL_DRUG)**[If an investigational drug or device is being used, add "[Name**

of drug/device] is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration." If the investigational drug/device is being compared to placebo, that should be mentioned in this introductory section.]
#end

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately **[number; Include screen failures who sign a consent]** people will take part in this study conducted by investigators at the University of Iowa. **[Add a sentence for the total number of subjects expected to participate nationwide, if a multi-site study.]**

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for **[Include the following in your description:**

- **Length of time for one subject's participation,**
- **If the study involves *more than one visit or contact*,**
  - **give the total number of visits,**
  - **approximate length of time for each visit (this can be a range such as "Visits will range from 4-8 hours in length"), and**
  - **if appropriate, length of time in between each visit**
- **If the study involves *long-term follow-up*, remember to include how long the subject will be followed, even if follow-up is based solely on clinical chart information with no direct subject contact.]**

WHAT WILL HAPPEN DURING THIS STUDY?

[Describe the following:

- **what is going to happen to the subject as part of this study**
  - **include a step-by-step outline of all procedures**
  - **include, in sequential order, how procedures will occur from the subject's point of view**
  - **write the procedures in "lay" language (do not use technical terms)**
  - **include subheadings, as appropriate**
- **what you are going to ask the subject to do if he/she participates**
  - **for complex protocols, consider including a chart or table showing which procedures/tests are performed at each visit. When using a table or chart, use the WORD software to create your tables/charts. Do NOT insert a "picture" of a table into the consent document.**
- **where the procedures will take place (e.g., outpatient clinic, inpatient unit, by mail, subject's home)**
- **any procedures, drugs, or devices that are experimental**
- ***if the study involves a screening visit* and includes tests or procedures that would *not* be done for clinical purposes, then Consent must be obtained prior to the screening visit.**

  - **Avoid wording such as "After the screening visit, if you are eligible to participate in the study, you will return for…" Rather, use wording such as "After the screening visit, if you are eligible to *continue* in the study, you will return for…" or "…if you are eligible to *receive the study treatment*, you will return for…"**
  - **The IRB considers the subject to be enrolled in the study as soon as the Consent is signed. The subject should be counted on Continuing Review applications, even if s/he is not eligible to continue in the study.**
- ***if the study involves surveys or questionnaires*, include a statement that the subject is free to skip any questions that he/she would prefer not to answer**
- ***HIPAA INFORMATION* (See also the WILL MY HEALTH INFORMATION BE USED… section):**
  - **include in your step by step procedures a specific and meaningful description of any past or present physical or mental health information that will be used as part of the study, and any future physical or mental health information that will be created during the research study.**
  - **describe the types of clinical procedures, laboratory tests, surgical procedures, imaging studies, etc. that will be used from the subject's existing medical record (e.g., your past medical history, your diagnosis, today's physical exam information, your height, weight, pulse, blood pressure, urinalysis results, etc.), or created and added to the subject's medical record or other hospital records during the course of the study procedures.**

#if($SSN_USAGE)***SOCIAL SECURITY NUMBER (SSN) USAGE***

You will be asked to provide your social security number on **[X document]** that is **[sent to X location or retained by the UI research team]**. The collection of your social security number is to **[insert reason here] [insert specific\exact information explaining how it will be used]** The collection of your social security number, **for research purposes other than payment**, is strictly optional and is not required for participation in the study.

____ I allow you to collect and use my social security number for the purposes outlined above.

____ I do NOT allow you to collect or use my social security number for the purposes outlined above. (Initial your choice above)
#end

Tissue/Blood/Data Storage for Future Use

[NEW COMMON RULE REQUIREMENT UNDER 45CFR46.116(b)(9), 45CFR46.116(c)(7), and 45CFR46.116(c)(9) will require this section to always be included in the informed consent document.

The following conditions must be explicitly stated in the informed consent document. The research team must carefully consider whether:

- **It *will\will not* be possible for future research use of tissue/blood/data to be performed.**
  - **Whether or not the use of tissue/blood/data *will\will not* include whole genome sequencing as part of the future use.**
- **Whether or not the tissue/blood/data will be stored *with\without* any identifiers or if it will be completely de identified.**
- **Whether the research *will\will not* include whole genome sequencing as part of this research.]**

[If tissue/blood/data WILL be collected for future use, include the following statements (NOTE: if the study is funded by a NIH grant, retention and sharing of data is REQUIRED and the below statements will be necessary. There must be disclosure to subjects about the possibility of submitting samples into the GWAS, dBGap, or other repositories sponsored by NIH.:]

As part of this study, we are obtaining **[insert specific type of tissue/blood/data – i.e., blood samples, tumor tissue]** from you. We would like to study your **[type of tissue/blood/data]** in the future, after this study is over. Your sample, information, and/or data may be placed in a central repository or other national repositories sponsored by the National Institutes of Health or other Federal agencies. If this happens, it may be stripped of identifiers (such as name, date of birth, address, etc). Other qualified researchers who obtain proper permission may gain access to your sample and/or data for use in approved research studies that may or may not be related to in the purpose of this study.

[If the future use of the blood samples will include making cell lines and DNA or conducting whole genome sequencing subjects must be informed. Insert the following paragraph as applicable:] Blood cells removed from the blood samples will be used to make a cell line and DNA or conduct whole genome sequencing. Cell lines are produced by growing blood cells in a laboratory and allow us to have a source of the DNA without having to redraw your blood. These blood cells can be stored for decades or more. The [**cell lines, DNA, and\or genome sequencing results]** and data will be made available to researchers trying to learn more about the cause of diseases.

[The next three paragraphs should only be inserted if genome sequencing is occurring] Each of the cells in your body contains DNA. DNA is the instruction manual that determines your appearance in things like eye color or how tall you can be. Your DNA may also lead to higher or lower risk of certain diseases. Your environment will also determine some of your disease risk.

Your DNA is a string of four building blocks, called "bases." These bases are represented by the letters G, A, T, and C. There are billions of these letters strung together in every human's DNA and they are

arranged in packages like words. Each of these "words" have specific jobs in the body. Most of the time the letters are the same in everyone. But about 1% of the population might have an "A" where someone else has a "G." This difference can explain why some people have blue eyes and others brown eyes, or why some have a high risk for a certain cancer and others a low risk. All these letters come together to create your "genome sequence", a kind of book of your genetics. It now possible to read off each of these letters and read your complete genome sequence. Your DNA sequence is unique to you. You inherit your DNA in almost equal parts from each of your parents. In very rare cases, your genome can also change through "mutations." A mutation is like if you tried to copy a page from a book, but misspelled some words. Mutations usually result from copying errors that occur in certain letters when being passed from parent to child.

When we take a sample of your blood/tissue for this study, it will go to a lab to read off those letters and give us a report on your genome. This information will then be compared with other genomes to see how they may be the same or different. It is our hope this will help us to better understand how the human body works and/or what causes it to not work well, as when someone has a disease.

The tests we might want to use to study your **[type of tissue/blood/data]** may not even exist at this time. Therefore, we are asking for your permission to store your **[type of tissue/blood/data]** so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding **[disease/condition]**, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your **[type of tissue/blood/data]** might be used to develop products tests, or discoveries that could be patented and licensed. In some instances, these may have potential commercial value and may be developed by the Investigators, University of Iowa, commercial companies, organizations funding this research, or others that may not be working directly with this research team. However, donors of **[type of tissue/blood/data]** do not retain any property rights to the materials. Therefore, there are no plans to provide financial compensation to you should this occur.

[Select one of the below paragraphs to reflect how the tissue/blood/data collected as part of the study will be identified\deidentified once it is collected.]

Your **[type of tissue/blood/data]** will be stored *with a code which may be linked to* **[insert what identifiers may be associated with the code (e.g. your name or any other kind of link that would enable us to identify which sample(s) are yours, DOB, etc)**]. If you agree now to future use of your **[type of tissue/blood/data]** but decide in the future that you would like to have it removed from future research, you should contact **[name and phone number of PI]**. However, if some research with your **[type of tissue/blood/data]** has already been completed, the information from that research may still be used.

--- OR ---

Your **[type of tissue/blood/data]** will be stored *without* your name or any other kind of link that would enable us to identify which sample(s) are yours. Therefore, if you give permission to store your **[type of tissue/blood/data]**, it will be available for use in future research studies indefinitely and cannot be removed.

[If subjects can participate in the main study without giving permission for future use of tissue/blood/data, consider using "yes/no" check boxes for the subject to indicate permission for the optional future use.

Examples of such "yes/no" options are given below: You may revise these to apply to your study.]

Please place your initials in the blank next to Yes or No for each of the questions below:

My [insert type [type of tissue/blood/data]] may be stored/shared for future gene research in _____. (e.g. cancer, heart disease, etc.)

_____ Yes _____ No

My [insert type of [type of tissue/blood/data]] may be stored/shared for future research for any other purpose.

____ Yes ____ No]
#end

WILL I BE NOTIFIED IF MY [DATA\BIOSPECIMENS\IMAGES] RESULT(S) IN AN UNEXPECTED FINDING?

[NEW COMMON RULE REQUIREMENTS UNDER 45CFR46.116(c)(8): a notice to subjects indicating if the study will\will not provide possible return of clinically relevant research results must now be included. If this will occur, additional information must be provided to explain how this communication will occur with the subject]

If clinically relevant research results WILL NOT be shared, include the following statement.

The results from the **[data/biospecimens/images]** we collect in this research study are not the same quality as what you would receive as part of your routine health care. The **[data/biospecimen/images]** results will not be reviewed by a physician who normally reads such results. Due to this, you will not be informed of any unexpected findings. The results of your **[data/biospecimens/images]** will not be placed in your medical record with your primary care physician or otherwise. If you believe you are having symptoms that may require care, you should contact your primary care physician.

OR

If clinically relevant research results WILL be shared, include the following statement.
We may learn things about you from the study activities which could be important to your health or to your treatment. If this happens, you can decide whether you want this information to be provided to you. If you choose to have this shared, you will be informed of any unexpected findings of possible clinical significance that may be discovered during review of results from your **[data/biospecimens/images]**. The results from the **[data/biospecimens/images]** we collect in this research study **[are/are not]** the same quality as what you would receive as part of your health care. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as feeling worried about a finding for which no treatment is

available). **[Insert a description of the types of research results which may be returned and how this will be communicated to subjects.]**

The **[data/biospecimens/images] [will/will not]** be reviewed by a physician who normally reads such results and they will inform us if there are any unexpected findings. We will provide you with this information so that you may discuss it with your primary care physician. However, if you believe you are having symptoms that may require care prior to receiving any information from this study, you should contact your primary care physician. The study team/study will not cover the costs of any follow-up consultations or actions.

Please initial one of the following options:

_____ Yes, I want to be provided with this information.
_____ No, I do NOT want to be provided with this information.

#if($GENETIC_RESEARCH)**Genetic Research**
One purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for the body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

You are being asked to give a **[insert type of sample, e.g. blood, urine, etc.]** for genetic research. What we learn about you from this sample will not be put in your health record. **[Note to investigators: Results of a genetic test may be given to subjects or placed in the medical record only if the test is performed in a CLIA-certified lab.] [If applicable, insert:** Your test results will not be shared with you or your doctor.**]** No one else (like a relative, boss, or insurance company) will be given your test results.

A single **[insert appropriate language, for example:**

- **blood sample of X teaspoons will be drawn from a vein in your arm using a needle; or**
- **cheek swab sample will be obtained by (indicate method); or**
- **urine sample will be obtained by (indicate method); or**
- **extra biopsy tissue will be obtained by (indicate method); or**
- **other (describe what other) sample will be obtained by (indicate method).**

This will take about **[X minutes/hours]** of your time.

[Results of a genetic test may be given to subjects or placed in the medical record only if the test is performed in a CLIA-certified lab. If receiving the results of the genetic test is optional, include a yes/no check box for subjects to indicate their choice. Also include whether or not genetic counseling would be available and who would pay for such counseling.]

Genetic Information Nondiscrimination Act (GINA)
A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Based on this new law, health insurance companies and group health plans are prohibited from requesting your genetic information that we get from this

research. This means that they may not use your genetic information when making decisions regarding your eligibility for insurance coverage or the amount of your insurance premiums. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. The law also does not prohibit discrimination if you are already known to have a genetic disease or disorder.
#end

#if($AV_USED)**Audio Recording/Video Recording/Photographs**
One aspect of this study involves making **[audio recordings / video recordings/photographs]** of you. **[Then describe why the recordings/photos are being made, who has access to them, and if or when they will be destroyed.]**

[If audio recording or video recording or photo is optional, (i.e., you would still enroll the subject in the study if s/he refused that aspect of the study), explain that the subject can still be in the study without being recorded or photographed, and add this statement:]
[ ] Yes [ ] No I give you permission to make **[audio recordings/ video recordings/ photographs]** of me during this study.
#end

#if($RESEARCH_TEAM_CONTACT)**[If you think you might contact your subjects again about being in one of your future studies, you should simply explain that possibility here including the information you plan to keep about them. In such cases, include information that agreeing to be in your current study does not obligate the subject to participate in one of your future studies, and that a separate Consent Document would be signed for future studies.]**
#end

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

**[*Describe the risks - physical, psychological, emotional, legal, privacy issues, etc.*

-Depending on the type of study, some risks may be better described as things that could make the subject "uncomfortable" – such as fatigue or embarrassment.

-There is no such thing as a "risk-free" study! If there are no known risks, state that there are "no foreseeable risks" to participating.

***If there are physical risks, format them either as a bulleted list or in table format as provided on the following pages.*]**

[Bulleted list format for physical risks:
Describe the condition/disease/indication in which these risks were experienced if different from the condition/disease/indication of this study.]

Likely / Common (more than 35%)
Life Threatening

- Risk 1
- Risk 2

Serious

- Risk 1
- Risk 2

Mild

- Risk 1
- Risk 2

Less Likely / Less Common (10% - 35%)

Life Threatening

- Risk 1
- Risk 2

Serious

- Risk 1
- Risk 2

Mild

- Risk 1
- Risk 2

Rare (less than 10%)

Life Threatening

- Risk 1
- Risk 2

Serious

- Risk 1
- Risk 2

Mild

- Risk 1
- Risk 2

[Table format for physical risks:
Describe the condition/disease/indication in which these risks were experienced if different from the condition/disease/indication of this study.]

Frequency of Risks	Mild	Serious	Life-Threatening
Likely\Common more than 35 %	• Risk 1 • Risk 2	• Risk 1 • Risk 2	• Risk 1 • Risk 2
Less Likely\Less Common 10-35 %	• Risk 1 • Risk 2	• Risk 1 • Risk 2	• Risk 1 • Risk 2
RARE less than 10 %	• Risk 1 • Risk 2	• Risk 1 • Risk 2	• Risk 1 • Risk 2

#if($GENETIC_RESEARCH)**Genetic Research**
One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only **[investigator's name and/or other's names]** will have access to your name.
#end

WHAT ARE THE BENEFITS OF THIS STUDY?

You will not benefit from being in this study.

--- OR ---

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because **[describe why others might benefit in the future in terms of the knowledge that will be gained. Note that compensation is not a benefit and should be described in the Costs and Compensation section.]**

WHAT OTHER TREATMENT OPTIONS ARE THERE?

[Include this section *only if the study involves treatment or therapy* for a disease or condition. Otherwise, DELETE this section!]

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could **[list the alternative treatments or procedures** #if($GCP) **AND any of the important potential benefits and risks of alternative treatments or procedures.** #end **If the subject can receive the same study treatment or therapy without being in the research, that must be disclosed.]**

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any **[costs/additional costs]** for being in this research study.

--- OR ---

You will have **[costs/additional costs]** for being in this research study. **[Clearly describe any costs to the subject:**

- **If research tests/procedures are conducted in a clinical setting, provide specific information about which tests/procedures would be covered by insurance and which would not be covered because they are for the research.**
- **Insurance co-payments should be described as a cost.**
- **When appropriate, consider adding a statement that the subject should talk to his/her insurance regarding coverage.**
- **If the sponsor is not paying for research tests or study treatments, consider adding a sentence instructing subjects to check with their insurance carrier prior to deciding whether to participate.]**

[For studies involving a clinical or therapeutic intervention, consider adding:]
You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

--- OR ---

You will be paid for being in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. You may also need to provide your address if a check will be mailed to you. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

[Clearly describe the monetary compensation:

- **total amount,**
- **average total amount,**
- **amount per visit,**
- **amount per hour, etc.).**

If compensation is pro-rated when a subject withdraws prior to completing the study, explain how it is pro-rated.]

[If there is non-monetary compensation (e.g., small gift, gift certificate), describe that separately from the monetary compensation statement.]

#if($CONFLICT_INTEREST)**DO THE RESEARCHERS HAVE PERSONAL FINANCIAL INTEREST IN THIS STUDY?**

[Name of researcher] [then describe the nature of the financial interest, e.g., is a paid consultant, owns stock in, is an officer of] a company called **[name]**. **[Name of researcher's]** financial relationship with this company has been reviewed by the University of Iowa's Conflict of Interest in Research Committee (CIRC). The CIRC has developed and implemented a plan to ensure that the research is conducted objectively.
#end

WHO IS FUNDING THIS STUDY?

#if($LOCAL_FUNDING)The University and the research team are receiving no payments from other agencies, organizations, or companies to conduct this research study.#end#if($FED_FUNDING)**[Name of agency/organization/company]** is funding this research study. This means that the University of Iowa is receiving payments from **[name]** to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from **[name]** for conducting this study.#end#if($GCRC_FUNDING)This research study will use the resources of the University of Iowa General Clinical Research Center (GCRC), which is funded by the National Institutes of Health (NIH). This means that the University of Iowa is receiving payments from the NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NIH for conducting this study.#end

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

[This section may be eliminated in most minimal risk studies – please contact the Human Subjects Office for guidance.]

[Include the following three bullets if your study WILL NOT have a contractual agreement with a sponsor to provide compensation for research-related illness or injury]:

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

--- OR ---

[The following four bullets MUST be used if your study WILL have a contractual agreement with a sponsor to provide compensation for research-related illness or injury]:

- If you are injured by or become ill from participating in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.

- The sponsor will reimburse your reasonable and necessary medical costs for treatment for a research-related illness or injury through the University of Iowa if the injury or illness :
  - is a direct result of the **[drug/device]** being studied or the properly performed study procedures
  - is not a medical condition that you had when you started the study;
  - is not the direct result of a failure to follow the study plan; and
  - is not the direct result of proven negligence of the University of Iowa.

- The sponsor does not plan to provide any other form of compensation to you for any illness or injury resulting from this study.

- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.

#if($NAME_KEPT)**WILL YOU KEEP MY NAME ON FILE TO GIVE TO OTHERS?**

We will keep information about you in a special kind of computer listing called a registry. A registry keeps information about you on file so that *other* researchers, not involved in this particular study, may contact you in the future about whether you are interested in being in *different* research studies. The registry will contain information such as your name, address, age, and selected medical information such as diagnosis and treatment. We will keep the information in this registry secure by **[method of security]**. You may request that your personal information be removed from this file at any time by contacting **[name, address, phone number]**

[If being in the registry is optional (i.e., you would still enroll the subject in the study even if s/he did not want to be placed in the registry), explain that the subject can still be in the study without being added to the registry, and add this statement:]

[ ] Yes [ ] No I give you permission to put my name and personal information in a registry so that other researchers can contact me in the future about different research studies.

#end

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- **[For drug/device studies, add: the U.S. Food and Drug Administration and the sponsor, (give company name)]**
- **[If applicable add: The sponsor (give company name) may also inspect any part of your medical record for the purposes of auditing the conduct of the study.]**
- **[For registry studies, add: people who use the registry]**,
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

#if($CTO_ADMIN)In the future, **[Name of sponsor/funding source]** may continue to use your health information that is collected as part of this study. For example, **[Name of sponsor/funding source]** may combine information from this study with the results of other studies to re-analyze the safety and effectiveness of the study **[device/medication]**, to evaluate other products or therapies, to develop a better understanding of a disease, or to improve the design of future research studies. **[Name of sponsor/funding source]** may also share information from the study with regulatory agencies in foreign countries.
#end
To help protect your confidentiality, we will **[describe the methods you will use to help ensure confidentiality. This description should agree entirely with the procedures described in Section X. of your HawkIRB application.]** If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

[If the Record of Informed Consent will be in the subject's UIHC medical record or the low risk database will be used, add the following:]
The University of Iowa Hospitals and Clinics generally requires that we document your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

#if($VII.B.1-if "clinical trial" is selected START HERE MICHAEL)

[If your trial will be required to be listed on ClinicalTrials.gov as an Applicable Clinical Trial (ACT), use the informed consent language below to meet the FDAA requirements found at http://www.gpo.gov/fdsys/pkg/FR-2011-01-04/pdf/2010-33193.pdf and 45 CFR 46.116(h) . IF FEDERAL FUNDING IS SUPPORTING THIS RESEARCH, a copy of the informed consent document must also be uploaded to the clinicaltrials.gov record. For additional information on the ClinicalTrial.gov reporting requirements, please visit the HSO website.]

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. [INSERT IF FEDERAL FUNDING] A copy of the informed consent document will be available on this website. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

[In addition, you may be responsible for registering your trial with ClinicalTrials.gov if:

- **You hold the Investigational New Drug Application (IND) or the Investigational Device Exemption (IDE) for your study**
- **Your study involves the UI serving as the coordinating center for a clinical trial under a prime award (as opposed to a subcontract)**
- **You do not hold the IND or IDE for your study, but you know that your Sponsor/funding agency has delegated you the responsibility to comply with the registration requirements (or if you can easily ascertain this from your contract or other award documentation)**
- **The clinical trial is regulated by the FDA (involves a drug, biologic or device), but does not require an IND/IDE]**

OR

POSTING OF THE INFORMED CONSENT DOCUMENT
[If the study does not meet the FDAA requirements of an Applicable Clinical Trial (ACT), but is a clinical trial, public posting of the clinical trial informed consent is required. Add the following language if the study is supported by a federal funding source:]

A version of the informed consent document will be available on the website, Regulations.gov (Docket ID: HHS-OPHS-2018-0021), as required by U.S. Law. The informed consent document will not include information that can identify you. You can search this website at any time.

#if($VII.B.1)**END HERE MICHAEL**

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?
[-Include this section if your study requires the use of a *health care provider's records concerning past, present, or future physical, dental, or mental health information about the subject.* If you use any past or present clinical information about someone, or if you add clinical information to a health care provider's record system (electronic or paper) during the course of the study, you should include this section.
-If using a health care provider's records is not required for your study (e.g., a self-report questionnaire only and no health information from paper or electronic health records will be included in your study data), then delete this section.
-If using a health care provider's records is optional in your study (i.e., you would enroll subjects who both *did* and *did not* give you permission to access their health records), contact the Human Subjects Office for advice on constructing this section of the Consent Document.

*****THIS SECTION MAY NOT BE MODIFIED IN ANY WAY. RELATED DETAILS ABOUT HOW STUDY DATA ARE BEING CODED, STORED, AND SHARED SHOULD BE ADDED TO THE CONFIDENTIALITY SECTION.***]**

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires **[use either "your health care provider" or the actual name of the entity holding the health records – e.g., University of Iowa Health Care, the College of Dentistry, Student Health, the College of Nursing, Wendell Johnson Speech & Hearing]** to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study **[if applicable, add: and for your treatment]**. Once **[use either "your health care provider" or the actual name of the entity, as above]** has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, **[list others with whom you may share study data, e.g., coordinating center, contract research** organization**, outside clinical laboratory, pharmaceutical company sponsor, device company sponsor, federal funding agency, colleagues at other institutions who are involved in this study, etc.]**.**[If applicable add: The sponsor (give company name) may also inspect any part of your medical record for the purposes of auditing the conduct of the study.]**

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes **[use "your health care provider" or the actual name of the entity, as above]** to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to **[PI name and address.]** However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

[For studies involving clinical or physical interventions, or if appropriate to your study, consider

adding these sub-sections:]

What if I Decide to Drop Out of the Study?

[Include the following if there are any adverse consequences (physical, social, economic, legal or psychological) of a subject's decision to withdraw from the research:]

Leaving the study early may cause you to experience the following harms or discomforts: **[Describe the adverse consequences (physical, social, economic, legal or psychological) of a subject's decision to withdraw from the research.]**

[Include the following if the protocol includes procedures for orderly termination of participation by the subject:]
If you decide to leave the study early, we will ask you to **[describe procedures for withdrawing, such as coming to a close out visit, and what that visit involves. Describe any other consequences of the subject's withdrawal.]**

[Include the following if there is a possibility that new information will be developed during the course of a study that may affect a subject's willingness to continue to take part:]

Will I Receive New Information About the Study while Participating?
If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

[Include the following whenever there are anticipated circumstances under which the subject's participation will be terminated by the investigator without regard to the subject's consent:]

Can Someone Else End my Participation in this Study?
Under certain circumstances, the researchers **[or the study sponsor]** might decide to end your participation in this research study earlier than planned. This might happen because **[describe why the study might be ended without the subject's consent, e.g., because in our judgment it would not be safe for you to continue, because your condition has become worse, because you are or became pregnant, because funding for the research study has ended, because the sponsor has decided to stop the research, etc.]**.

#if($PRISONERS)**SPECIAL INFORMATION FOR PRISONERS WHO PARTICIPATE IN THIS STUDY**

If you take part in this research study, your participation will not affect or influence the length of your sentence, your parole, or any other aspect of your incarceration. Likewise, if you decide not to participate, or if you leave the study before it is over, that will not be held against you. **[If applicable, add: If you complete your sentence while participating in this study, you may continue to participate afterwards. (Then describe how participation would continue if the prisoner is**

released during the study. Also describe any changes in Costs and Compensation that may occur should the subject be released from prison during the course of the study.)]
#end

FOR IRB USE ONLY
$STAMP_IRB
$STAMP_IRB_ID
$STAMP_APPRV_DT

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: **[name(s), phone number(s)].** If you experience a research-related injury, please contact: **[name(s), phone number(s)]**. **[If study involves significant risks, include 24/7 phone number, instructions about who to ask for (e.g., research fellow on call, resident on call, etc.), and to tell operator you are a research subject. *If PI is a student*, the name and contact information for the supervising faculty member should be included.]**

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

#if($CONSENT_OBTAINER_NEEDED)This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after $STAMP_EXP_DT.

_____ _____

(Signature of Subject) (Date)

FOR IRB USE ONLY
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#if($PARENT_SIGNATURE_NEEDED)Parent/Guardian or Legally Authorized Representative's Name and Relationship to Subject:

_____ _____
(Name - printed) (Relationship to Subject - printed)

Do not sign this form if today's date is on or after $STAMP_EXP_DT.

_____ _____
(Signature of Parent/Guardian or Legally Authorized Representative) (Date)

Legally Authorized Representative:
In studies conducted in the state of Iowa, the first person on the list below who is reasonably available and competent must sign as the legally authorized representative even if another person on the list is more conveniently available.

1. The designated proxy (such as a Durable Power of Attorney for Health Care)
2. Court-appointed guardian
3. Spouse (does not include "Common-law" spouse)
4. Adult child
5. Parent
6. Adult sibling

#end

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)
#end

APPENDIX

SUGGESTED WORDING FOR SPECIFIC ISSUES

These paragraphs should be cut and pasted into the appropriate area of the Consent Document.

The suggested wording below should be modified appropriately for the specifics of your study!!

Suggested text box to add after the Research Team Contact listing at the beginning of the consent document when a legally authorized representative will be signing the consent document.

If you are the legally authorized representative of a person who is being invited to be in this study, the word "you" in this document refers to the person you represent. You will be asked to read and sign this document to give permission for the person you represent to participate in this research study.

[Insert this section PRIOR to the WHAT WILL HAPPEN section when minor subjects will be required to have pregnancy testing during screening or as part of study procedures.]

Pregnancy Testing for Females Under the Age of 18

All females who are physically able to become pregnant will be required to have a pregnancy test before **[describe each time the testing will occur in relation to study procedures]**. If the test shows that you are pregnant, you will not be able to **[have this test/continue in the study.]** This testing will occur in a private area without any of your family members with you.

- If you are 12 years of age or older we will only tell you the results of the test.
  - You can decide whether or not to tell your parents or guardian the results of the pregnancy test, however, if you are pregnant we will need to tell your parents you cannot **[have – fill in the study procedure/continue in the study.]**
  - If the pregnancy test shows that you are pregnant we will ask you whether or not you want us to talk with your parents or guardian about your pregnancy.

- If you are under 12 years of age and the pregnancy test shows that you are pregnant, we are required to report the pregnancy to the proper authorities.

- **IMPORTANT:** No matter how old you are - if we think that your pregnancy may have happened because of abuse, we will tell the proper authorities and your parents or guardian will be told about your pregnancy.

1. WHAT WILL HAPPEN? section:

Randomized Clinical Trials
[Suggested text for the What Will Happen section – does not need separate heading:]
You will be randomly assigned to receive one of the **[number]** study treatments, either **[name the study**

treatments]. This means that whichever study treatment you receive will be determined purely by chance, like flipping a coin. You will have a **[give the odds of being in any study group – 50/50, 1 out of 3, etc.]** chance of receiving any one of the study treatments. **[For double-blind studies:]** Neither you nor the research team will know which study treatment you are receiving, but we will be able to get this information quickly if we need it to ensure your safety.

MRI Scans

[Suggested text for the What Will Happen section – does not need separate heading:]
An MRI scanner takes pictures of the inside of your body by sending out a magnetic field and radio waves. Because the MRI scanner contains a very strong magnet, you may not be able to have the MRI if you have certain kinds of metal in your body (for example, a heart pacemaker, a metal plate, certain types of heart valves or brain aneurysm clips). Someone will ask you questions about this before you have the MRI.

The MRI scanner is a large machine that contains a hollow tube. You will be asked to lie on your back on a special table that slides into the tube. The sides of the tube will be fairly close to your body and the scanner makes a loud hammering noise while you are inside. You will be able to talk to people in the room through a speaker system. We will monitor you closely while you are inside the scanner.

Imaging Studies

[The following is suggested text for the What Will Happen section and it does not need a separate heading. You should include this text for research studies involving imaging that are performed in ways that are adequate for answering the research questions, but are not as comprehensive as a clinical study using the same modality would be. Often, these research images are not officially read by a radiologist, and there is no report placed in the medical record.]:

The **[insert name of imaging study, e.g. MRI, CT, PET etc]** images for this study are not being used to evaluate your health. The images obtained for this study are for specific research purposes and are not being used to find medical abnormalities. These images will not be reviewed by a radiology physician to diagnose existing abnormalities.

2. WHAT ARE THE RISKS? section:

Placebo

[Add to text of the standard Risks section – does not need separate heading:]
You may receive a placebo (an inactive substance) during this study. This means that you would receive no active study treatment while participating and your **[symptoms / disease]** could get worse.

Women Capable of Becoming Pregnant

If you are a woman who is capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to your fetus, or risks to your fetus that we did not anticipate, associated with being in the study. There may be

long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. If you believe or know you have become pregnant while participating in this research study, please contact **[name and phone number]** as soon as possible.

Radiation Exposure in Women Capable of Becoming Pregnant

You may not participate in this study if you are pregnant. If you are capable of becoming pregnant, we will perform a pregnancy test before exposure to research-related radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

Testing for Reportable Diseases

[For a link to a listing of reportable diseases in the state of Iowa, please refer to the Iowa Department of Health listing]

If you decide to participate in this study, we will test you for **[name of disease]**. **[If the test requires a separate consent, add the following sentence:]** We will ask you to sign a separate consent form for this test. The results of the test could indicate that you have **[name of disease]**. If that happens, we will refer you to a doctor who specializes in treating **[name of disease]**. We will make every effort to keep your personal information confidential. However, we are required by law to report positive tests to the Iowa Department of Public Health. Becoming aware of a diagnosis of **[name of disease]** could have serious personal and/or social consequences, including difficulty obtaining health insurance or employment. For more information about the risks of **[name of disease]** testing, please talk to your study doctor.

MRI Scan

You may be uncomfortable inside the MRI scanner if you do not like to be in closed spaces ("claustrophobia"). During the procedure, you will be able to talk with the MRI staff through a speaker system. You can tell them to stop the scan at any time.

The MRI scanner produces a loud hammering noise, which has produced hearing loss in a very small number of patients. You will be given earplugs to reduce this risk.

[If applicable:] If you have claustrophobia, you may require medication to help you relax ("sedation"). If you do require medication to relax, you should not drive a car, take part in activities like riding a bike, or perform other similar tasks until the next morning, because the medication(s) can affect your thinking for several hours and can slow down your reflexes.

3. WHAT ABOUT CONFIDENTIALITY? section:

Certificate of Confidentiality

[Certificate of Confidentiality – [IF THE RESEARCH IS FUNDED BY NIH, DETERMINE WHETHER CoC CRITERIA APPLY. IF YES, X.7 SHOULD BE YES AND THE BELOW LANGUAGE IS REQUIRED.] Delete the standard Confidentiality text from regular template, and replace with:]

It is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- **[For drug/device studies, add: the U.S. Food and Drug Administration and the sponsor, (give company name)]**
- **[For registry studies, add: people who use the registry]**,
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will **[describe the methods you will use to help ensure confidentiality. This description should agree entirely with the procedures described in Section X. of your HawkIRB application.] [If there is a physical interaction or collection of physical specimens on the UIHC premises, add the following: A Record of Informed Consent document will be placed in your UIHC medical record to show that you have participated in this research study.]**

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

To further protect your privacy, the researchers have obtained a Certificate of Confidentiality from the Department of Health and Human Services (DHHS). This Certificate means that the researchers cannot be forced (for example by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding. However, a Certificate of Confidentiality does not prohibit the researcher from disclosing information about you or your involvement in this research that you have agreed to disclose or make available. For example, if you **[if applicable: or your legally authorized representative]** request in writing that information about you or your participation in the research be released to an insurance company, the researcher may not use the Certificate of Confidentiality to withhold this information. This means that you and your family should actively protect your own privacy. Finally, the researcher is not prevented from taking steps, including reporting to appropriate authorities, to prevent serious harm to yourself or others. You may receive a copy of the Certificate of Confidentiality upon request.

Studies Focusing on Violence, Abuse, or Self-Inflicted Injury

[Add this sentence to the text of the standard Confidentiality section – does not need heading:] We will disclose to the proper authority information you share with us concerning child abuse, child sexual abuse, or harming yourself or others.

Person Who Obtained Consent Signature Template (By Mail or in Person)

When a mail-out consent process will be used and the research team will not discuss the study with the potential subject, the Person Who Obtained Consent (PWOC) signature block should be omitted from the Informed Consent Document.

When the research team will obtain consent by mail and, if there is a possibility that a research team

member may discuss the study with the potential subject, the following PWOC signature block section may be added below the subject signature block and the appropriate action will be selected on an individual basis:

Add this section below the subject signature block in place of the current Statement of Person Who Obtained Consent:

Check the method by which consent is being obtained:
□ Consent is being obtained by mail without a discussion between a research team member and the subject. (Research team member does not sign this document)

□ Consent is being obtained in person or by mail after a discussion between a research team member and the subject. (Research team member signs below.)

Statement of Person Who Obtained Consent
(This line is only to be signed by a research team member after discussion with subject.)

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person Who Obtained Consent) (Date)

If no discussion occurs, the research team member will check the first box and the PWOC signature/date line will not be completed. (The best practice is for the research team member to document the date the consent was received on the Informed Consent Document or in the research records, and to sign and date the entry.)

If a member of the research team discusses the study with the individual, the second box will be checked and the research team member will sign the PWOC line and include the date the Informed Consent Document was received. (The best practice is for the research team member to document the date the discussion occurred, as well as the date the consent was received on the Informed Consent Document or in the research records, and to sign and date the entry.)

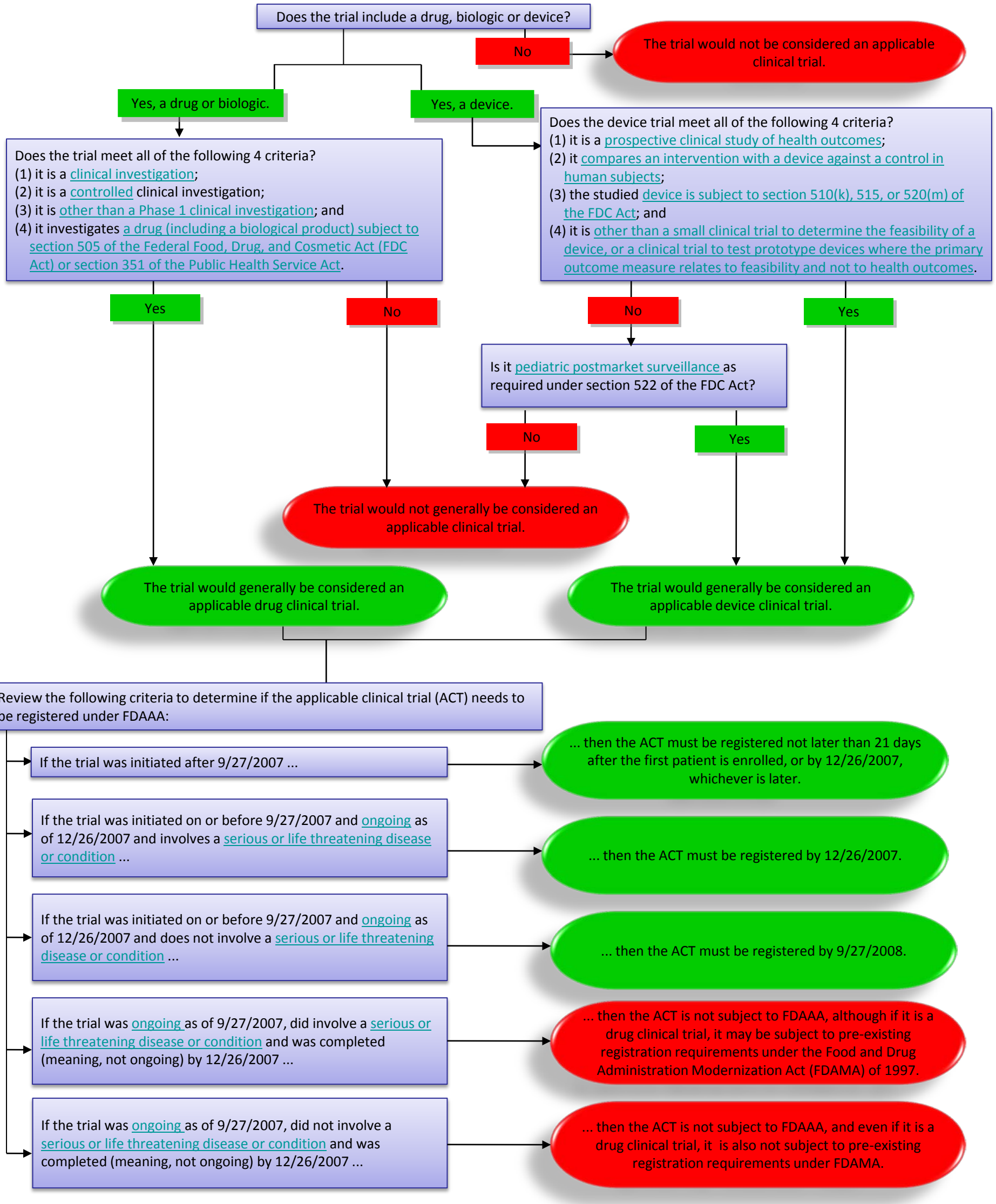
Significant Differences in FDA and HHS Regulations for Protection of Human Subjects

- HHS regulations apply to research conducted by the HHS or funded in whole or in part by the HHS.
- FDA regulations apply to research involving products regulated by the FDA.
- Federal support is not necessary for the FDA regulations to be applicable.
- When research involving products regulated by the FDA is funded, supported or conducted by FDA and/or HHS, both the HHS and FDA regulations apply.

Differences	**HHS (45 CFR 46)**	**FDA (21 CFR 50 & 21 CFR 56)**
Definitions: See Appendix I in this Manual	46.102	56.102
General Requirements for Informed Consent & Emergency Use – Consent Elements	46.116 46.116(a)(5)	56.104 56.23 50.25(a)(5)
Waiver of Elements of Consent – See Waivers	46.116(c)&(d)	N/A
Exempt from regulations	46.101 HHS exempts certain categories of research & provides for a Secretarial waiver	56.105 FDA provides for sponsors & sponsor-investigators to request a waiver of IRB review requirements (but not informed consent requirements).
Waiver of documentation of consent – See Waivers	46.109 & 46.117(c)	56.109 50.27
Expedited Review of Research --	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.	56.110 The FDA list of investigations eligible for expedited review (published in the Federal Register) does not include the studies described in category 9 of the HHS list because these types of studies are not regulated by FDA
Cooperative Research – Both regulations make allowances for the review of multi-institutional studies.	46.114	56.114: FDA does not discuss administrative matters dealing with grants & contracts because they are irrelevant to the scope of the FDA's regulation.
IRB Records – 46.115 v. 56. 115	FDA has neither an assurance mechanism (FWA) nor files of IRB membership (IRB registration). Therefore, FDA does not require the IRB or institution to report changes in membership whereas HHS does require such notification.	

Identifying an "Applicable Clinical Trial" under FDAAA

- This flowchart presents basic guidance on determining if a trial is considered an "applicable clinical trial" under FDAAA. It maps out the guidance provided in the "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial", and is also available as an interactive flowchart at: http://grants.nih.gov/ClinicalTrials_fdaaa/index.htm
- This flow chart may not address every situation. The grantee's sponsored research office, general counsel, or other similar official should be involved in determining whether or not the grant supports an applicable clinical trial that needs to be registered under FDAAA.



Human Subject Regulations Decision Charts

February 16, 2016

The Office for Human Research Protections (OHRP) provides the following graphic aids as a guide for institutional review boards (IRBs), investigators, and others who decide if an activity is research involving human subjects that must be reviewed by an IRB under the requirements of the U.S. Department of Health and Human Services (HHS) regulations at 45 CFR part 46. OHRP welcomes comment on these decision charts. The charts address decisions on the following:

- whether an activity **is research** that must be reviewed by an IRB
- whether the review may be performed by **expedited procedures**, and
- whether **informed consent** or its documentation may be waived.

Considerations

The charts are intended to assist IRBs, institutions, and investigators in their decision-making process and should not be used as substitutes for consulting the regulations. OHRP cautions that the full text of applicable regulatory provisions should be considered in making final decisions.

These charts are necessarily generalizations and may not be specific enough for particular situations. Other guidance documents are available related to specific topics, at OHRP Policy Guidance by Topic. OHRP invites inquiries for additional information.

The charts do not address requirements that may be imposed by other organizations, such as the Food and Drug Administration, National Institutes of Health, other sponsors, or state or local governments.

Chart 1: Is an Activity Research Involving Human Subjects?

Chart 2: Is the Human Subjects Research Eligible for Exemption?

Chart 3: Does Exemption 45 CFR 46.101(b)(1) (for Educational Settings) Apply?

Chart 4: Does exemption 45 CFR 46.101(b)(2) or (b)(3) (for Tests, Surveys, Interviews, Public Behavior Observation) Apply?

Chart 5: Does Exemption 45 CFR 46.101(b)(4) (for Existing Data, Documents, Records and Specimens) Apply?

Chart 6: Does Exemption 45 CFR 46.101(b)(5) (for Public Benefit or Service Programs) Apply?

Chart 7: Does Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies) Apply?

Chart 8: May the IRB Review Be Done by Expedited Procedures?

Chart 9: May the IRB Continuing Review Be Done by Expedited Procedures?

Chart 10: May Informed Consent Be Waived or Consent Elements Be Altered under 45 CFR 46.116(d)?

Chart 11: May Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?

Chart 1: Is an Activity Research Involving Human Subjects Covered by 45 CFR part 46?

February 16, 2016

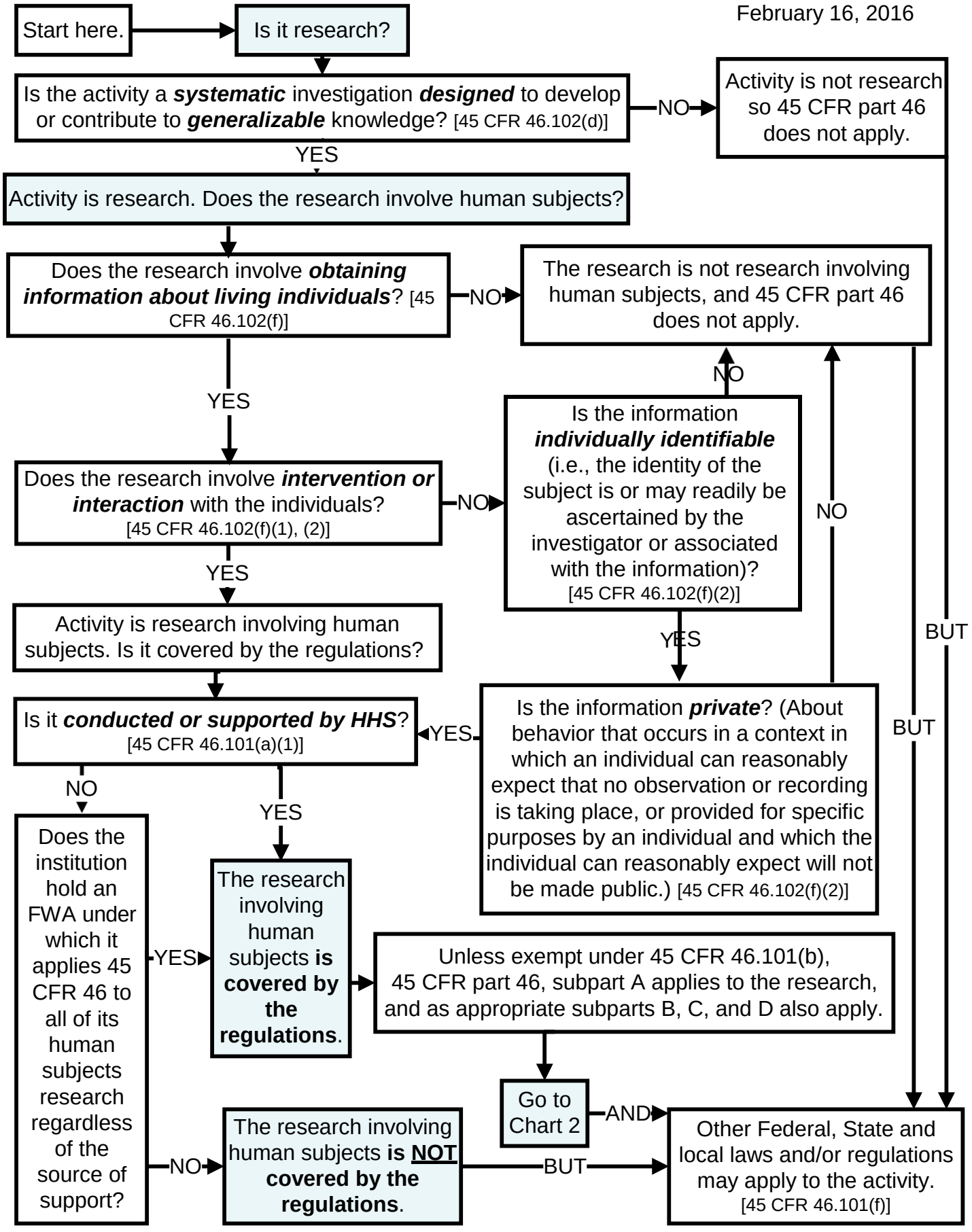


Chart 2: Is the Research Involving Human Subjects Eligible for Exemption Under 45 CFR 46.101(b)?

From Chart 1

February 16, 2016

Has HHS ***prohibited*** exemption of the human subjects research? (All research involving prisoners, some research involving children.) [Footnote 1 to 45 CFR 46.101(i), 45 CFR 46.401(b)]

YES → Go to Chart 8

NO

Will the ***only**** involvement of human subjects be in one or more of the following categories?

*** *"Only"*** means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is ***not*** exempt.

Research conducted in ***established or commonly accepted*** educational settings, involving ***normal education practices***?

YES → Exemption 45 CFR 46.101(b)(1) may apply. → Go to Chart 3

If not exempt under (b)(1)

Research involving the use of ***educational tests, survey procedures, interview procedures, or observation of public behavior***?

YES → Exemption 45 CFR 46.101(b)(2) or (b)(3) may apply. → Go to Chart 4

If not exempt under (b)(2) or (b)(3)

Research involving collection or study of ***existing*** data, documents, records, or pathological or diagnostic specimens?

YES → Exemption 45 CFR 46.101(b)(4) may apply. → Go to Chart 5

If not exempt under (b)(4)

Research studying, evaluating, or examining ***public benefit or service programs***?

YES → Exemption 45 CFR 46.101(b)(5) may apply. → Go to Chart 6

If not exempt under (b)(5)

Research involving ***taste and food quality evaluation*** or ***consumer acceptance studies***?

YES → Exemption 45 CFR 46.101(b)(6) may apply. → Go to Chart 7

If not exempt under (b)(6)

No exemptions to 45 CFR part 46 apply.
Provisions of 45 CFR subpart A apply, and subparts B, C and D also apply if subjects are from covered vulnerable populations. → Go to Chart 8

Chart 3: Does Exemption 45 CFR 46.101(b)(1) (for Educational Settings) Apply?

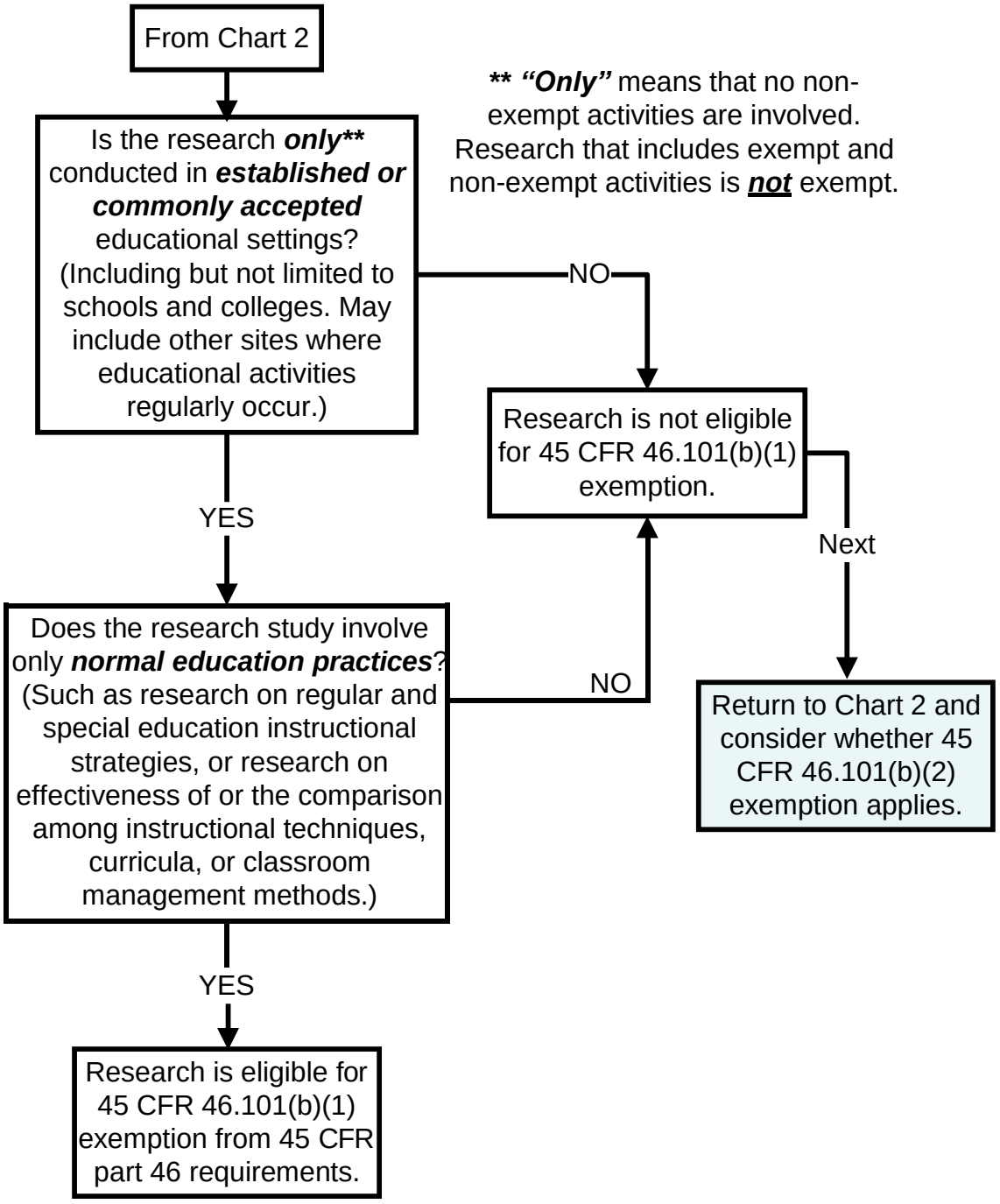


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Chart 4: Does Exemption 45 CFR 46.101(b)(2) or (b)(3) (for Tests, Surveys, Interviews, Public Behavior Observation) Apply?

February 16, 2016

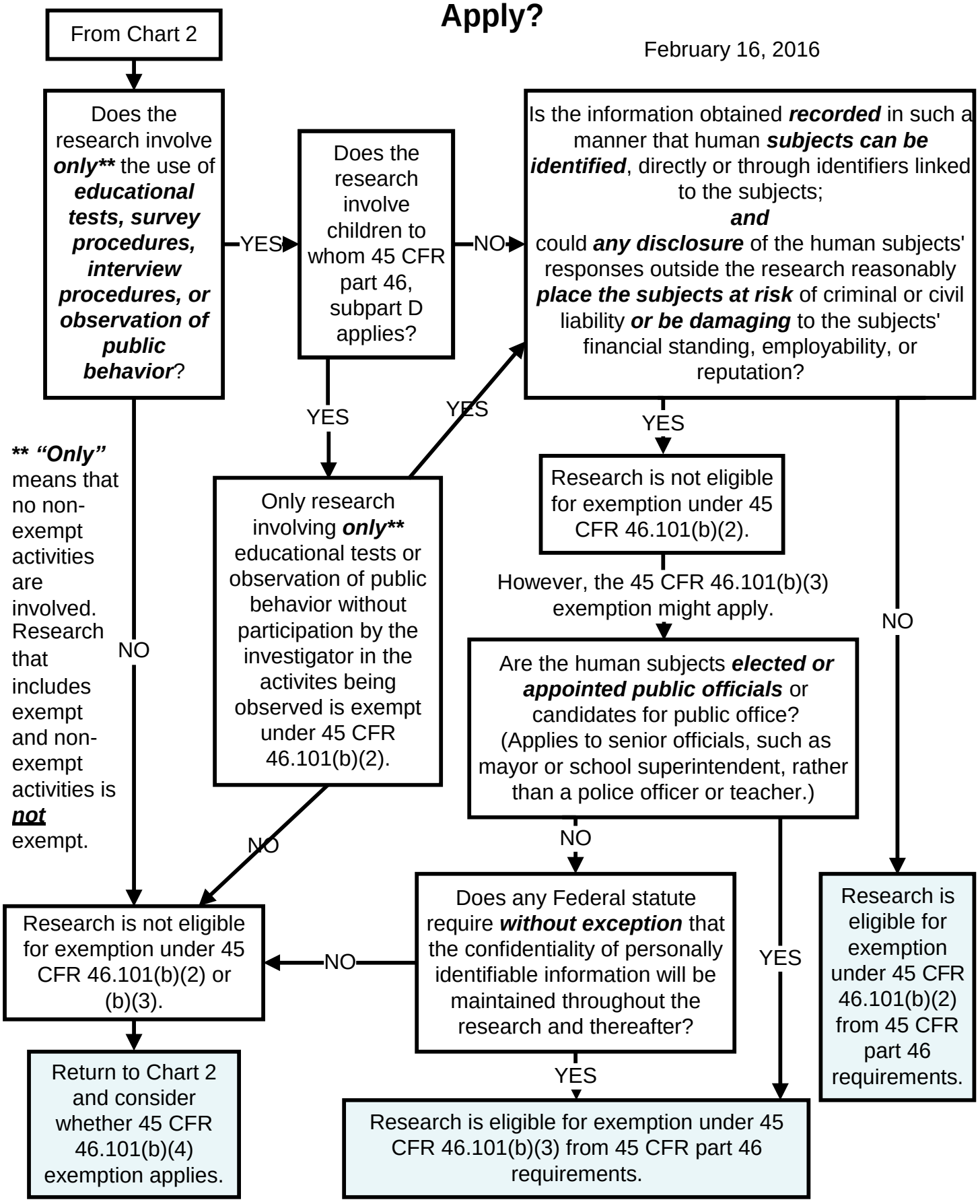
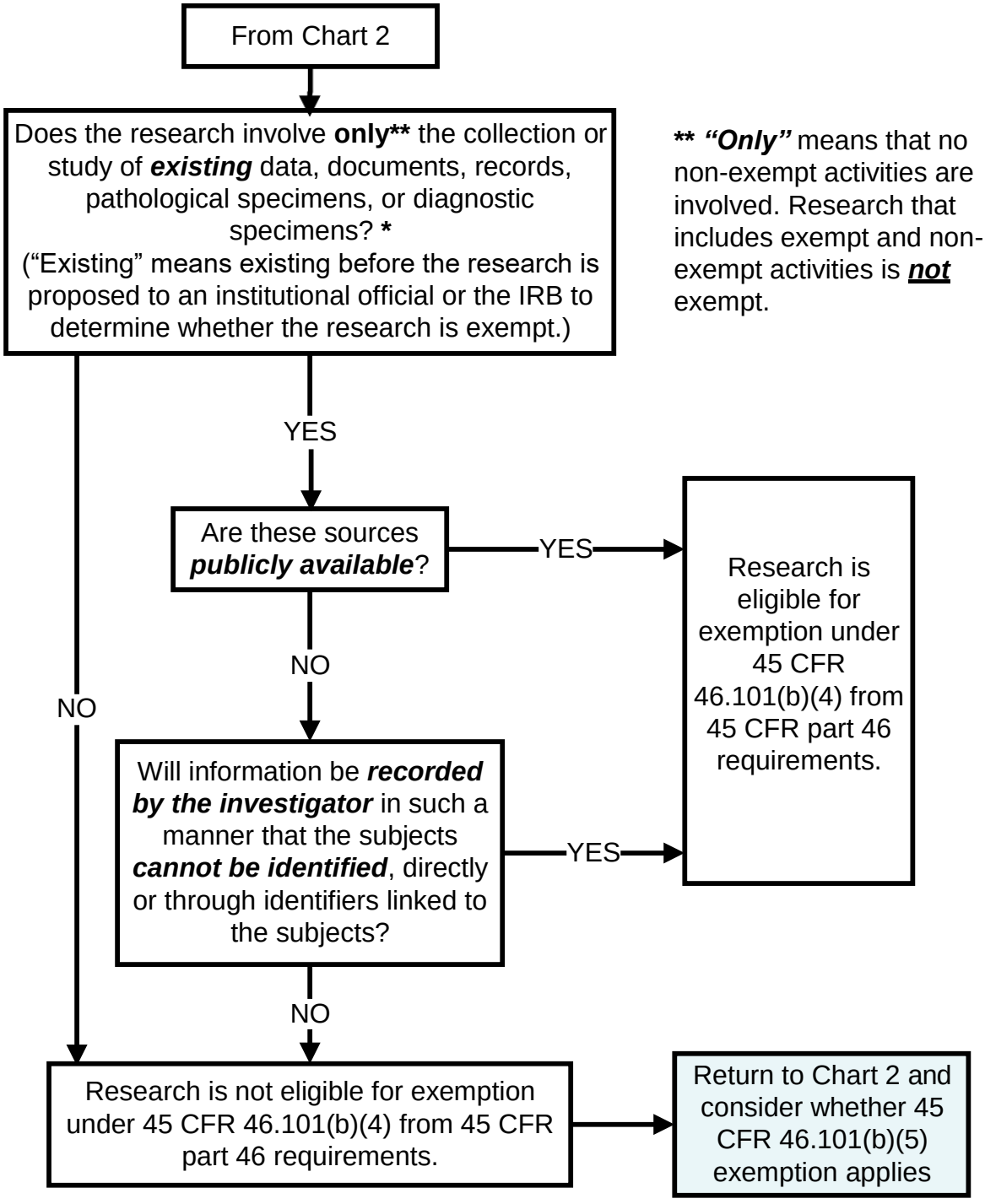


Chart 5: Does Exemption 45 CFR 46.101(b)(4) (for Existing Data Documents and Specimens) Apply?



** ***"Only"*** means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is ***not*** exempt.

* Note: See **OHRP** guidance on research use of stored data or tissues and on stem cells at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-research-involving-stem-cells/index.html, and on coded data or specimens at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html for further information on those topics.

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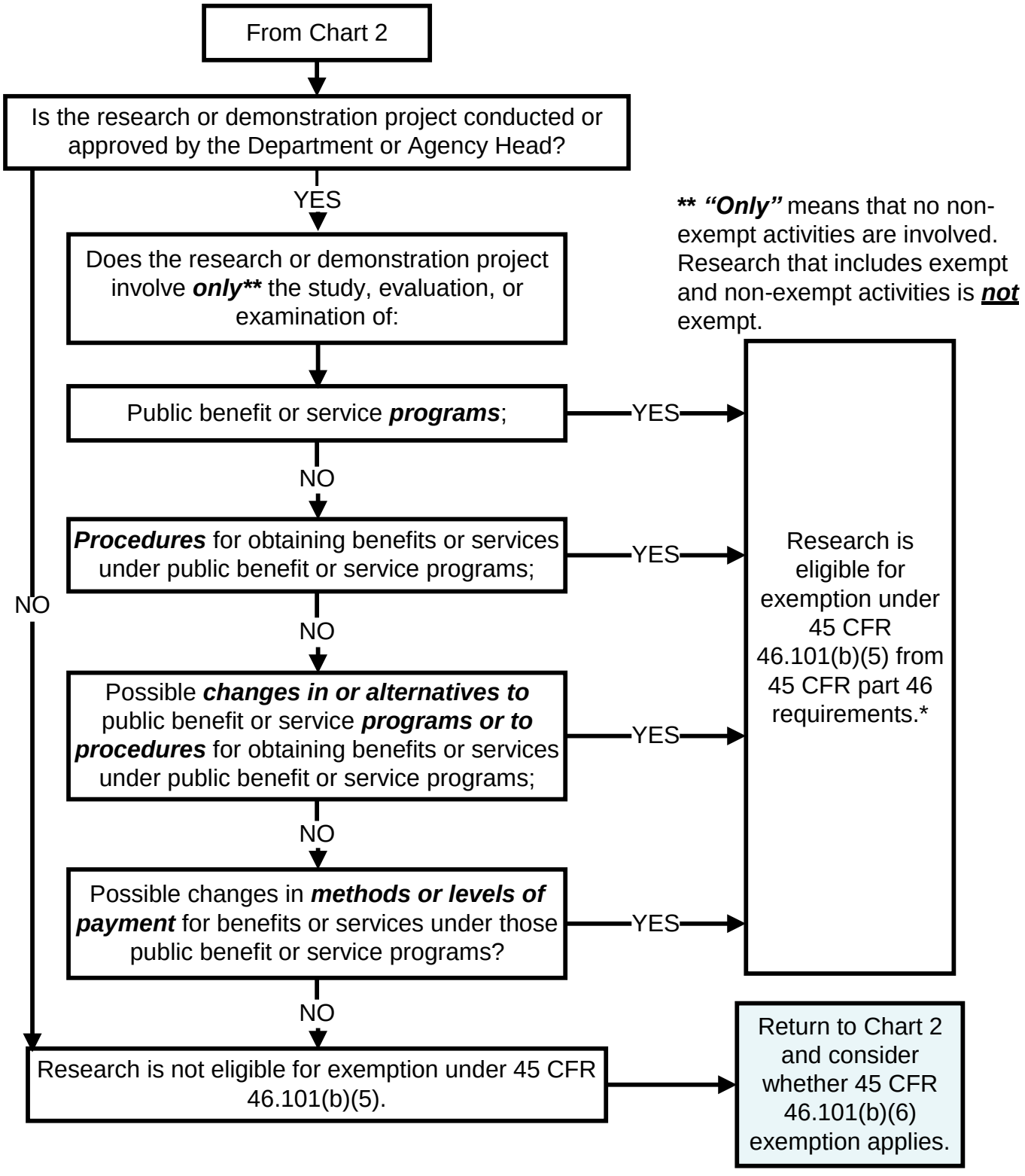
Chart 6: Does Exemption 45 CFR 46.101(b)(5) (for Public Benefit or Service Programs) Apply?



** ***"Only"*** means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is ***not*** exempt.

* Note: See **OHRP** guidance on exemptions at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/exemptions-for-public-benefit-and-service-programs/index.html for further description of requirements for this exemption.

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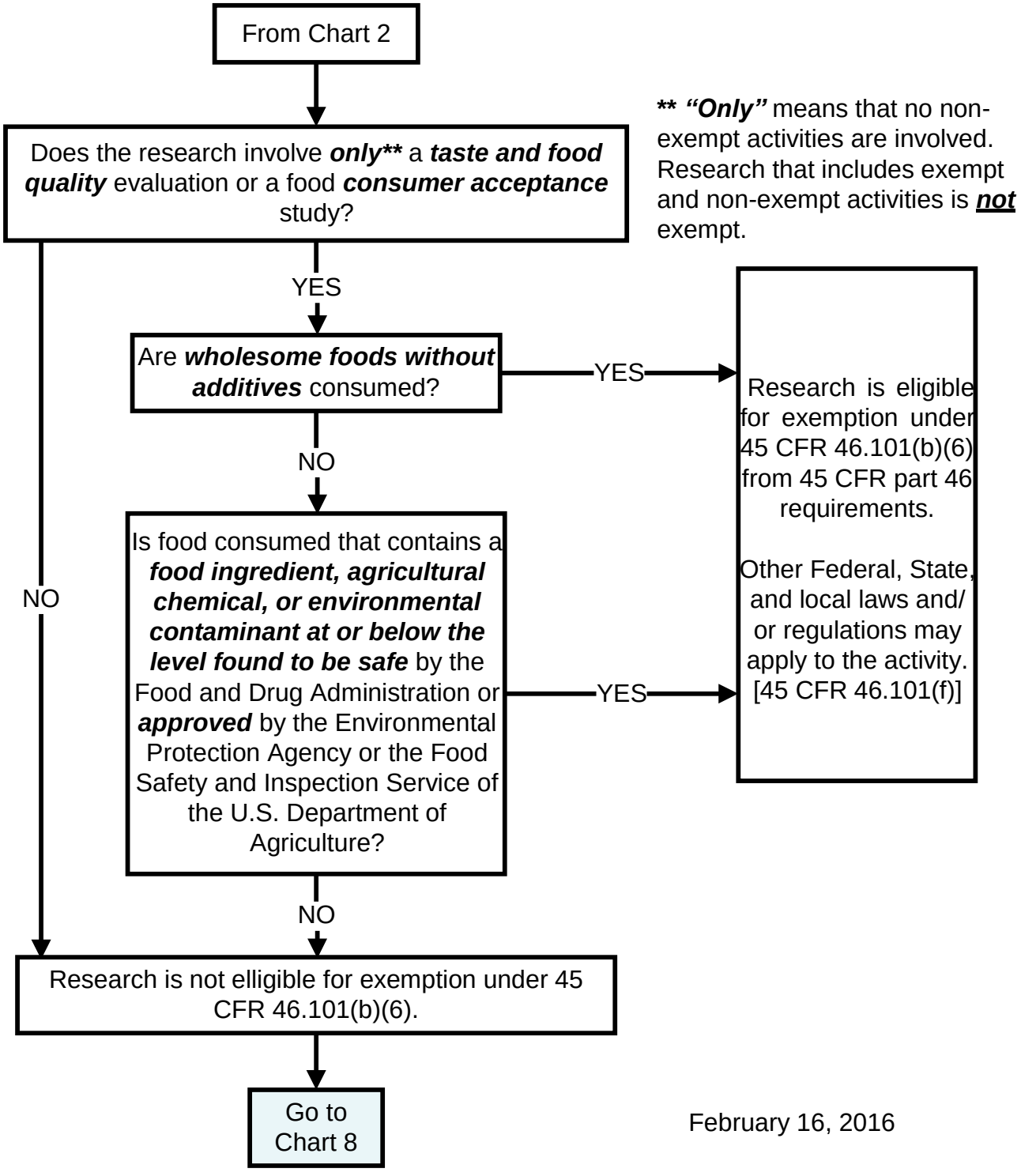
Chart 7: Does Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies) Apply?



** ***"Only"*** means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is ***not*** exempt.

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Chart 8: May the IRB Review Be Done by Expedited Procedures Under 45 CFR 46.110?*

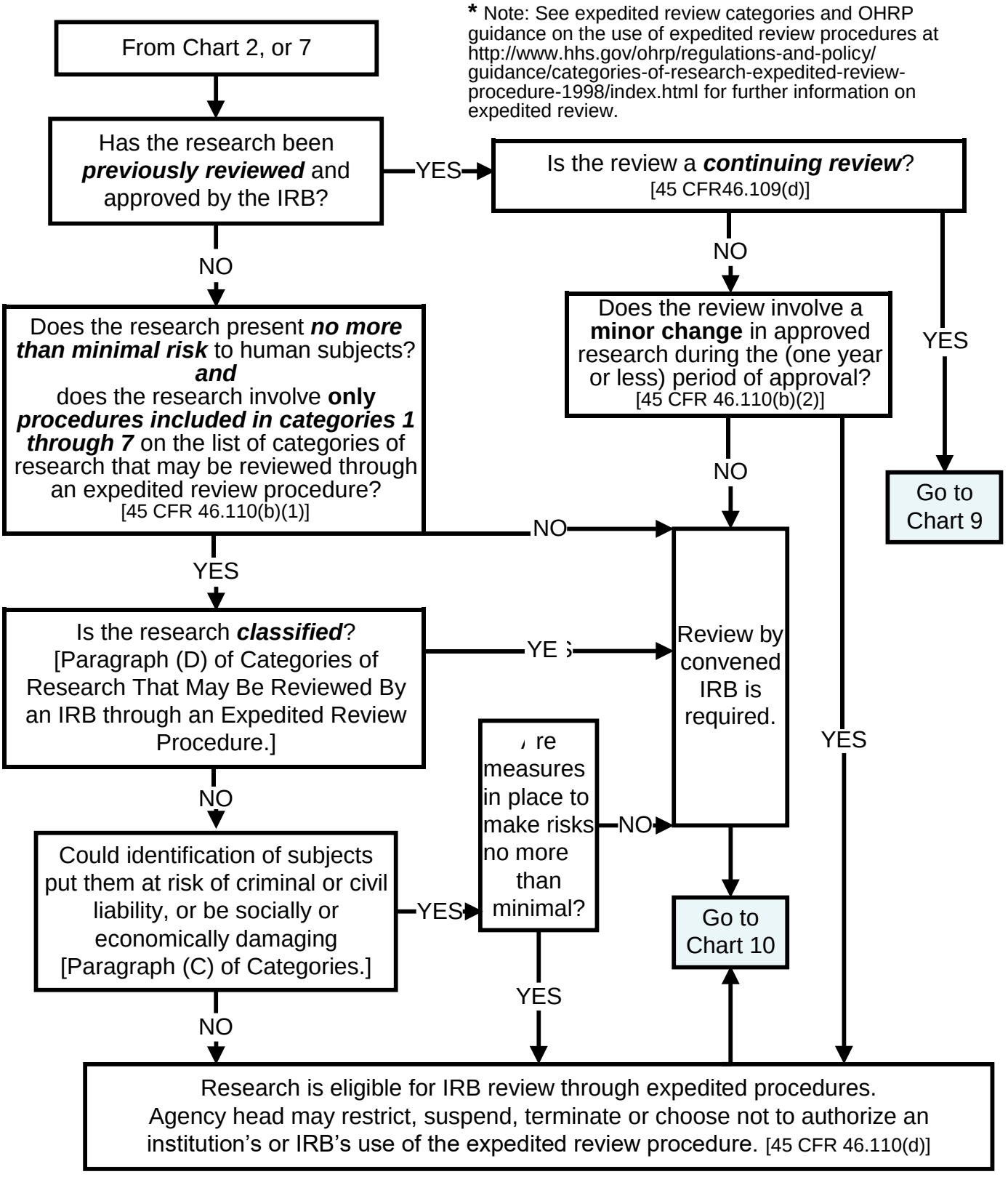

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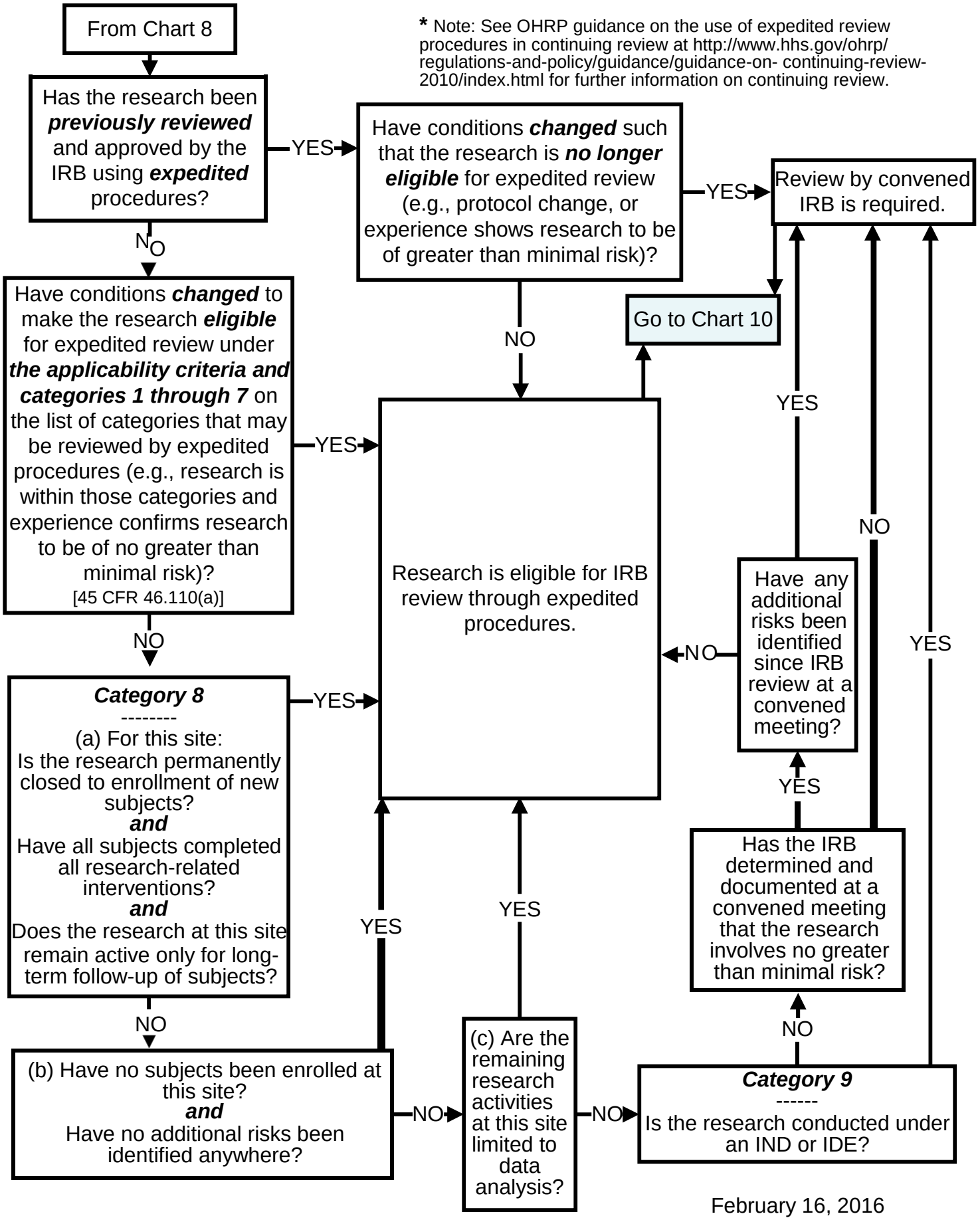
Chart 9: Can Continuing Review be Done by Expedited Procedures Under 45 CFR 46.110?



***** Note: See OHRP guidance on the use of expedited review procedures in continuing review at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on- continuing-review-2010/index.html for further information on continuing review.

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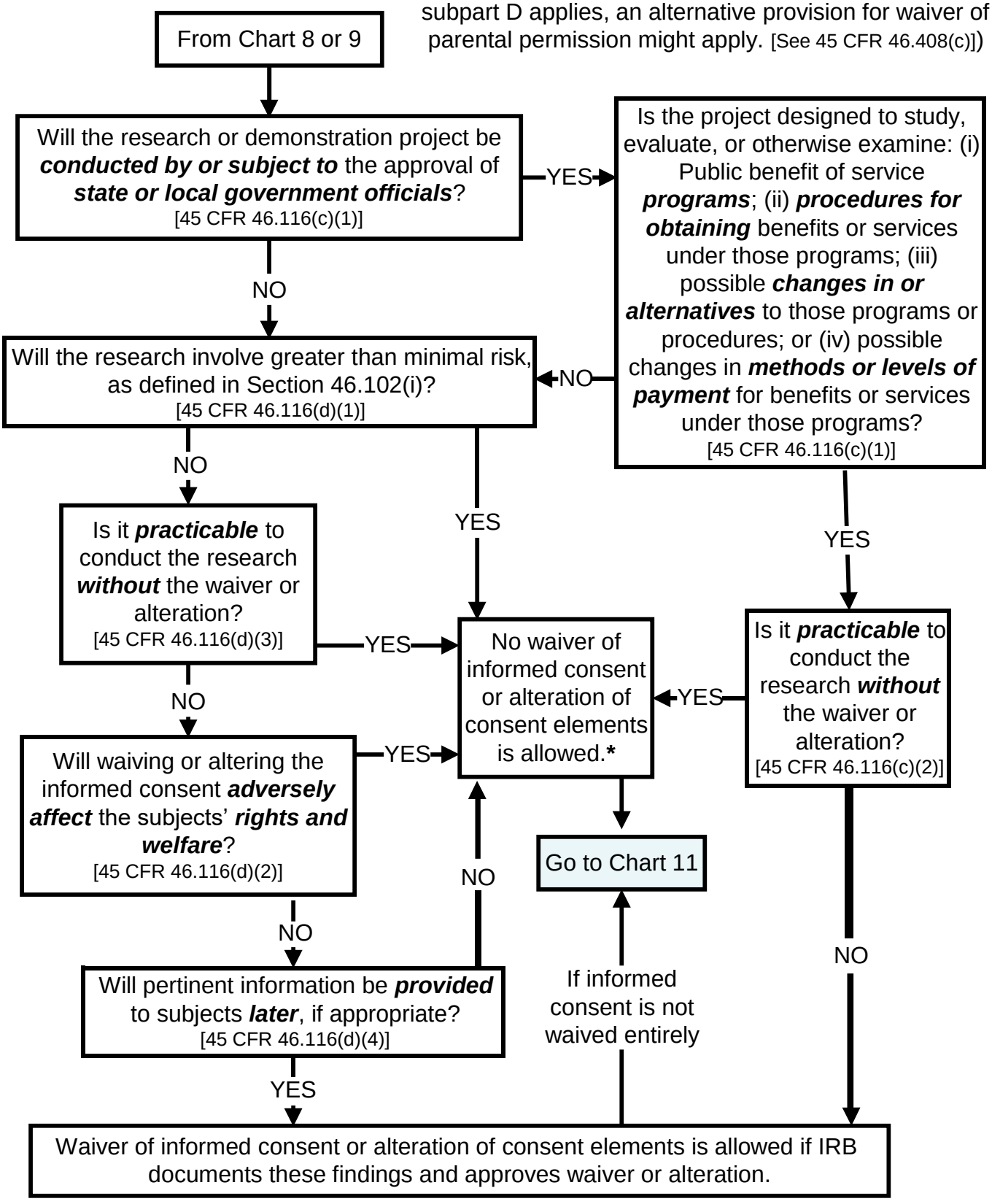
Chart 10: Can Informed Consent Be Waived or Consent Elements Be Altered Under 45 CFR 46.116(c) or (d)?**

**(Note: If subjects include children to whom 45 CFR part 46, subpart D applies, an alternative provision for waiver of parental permission might apply. [See 45 CFR 46.408(c)])



* Note: See OHRP guidance on informed consent requirements in emergency research at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/emergency-research-informed-consent-requirements/index.html for further information on emergency research informed consent waiver.

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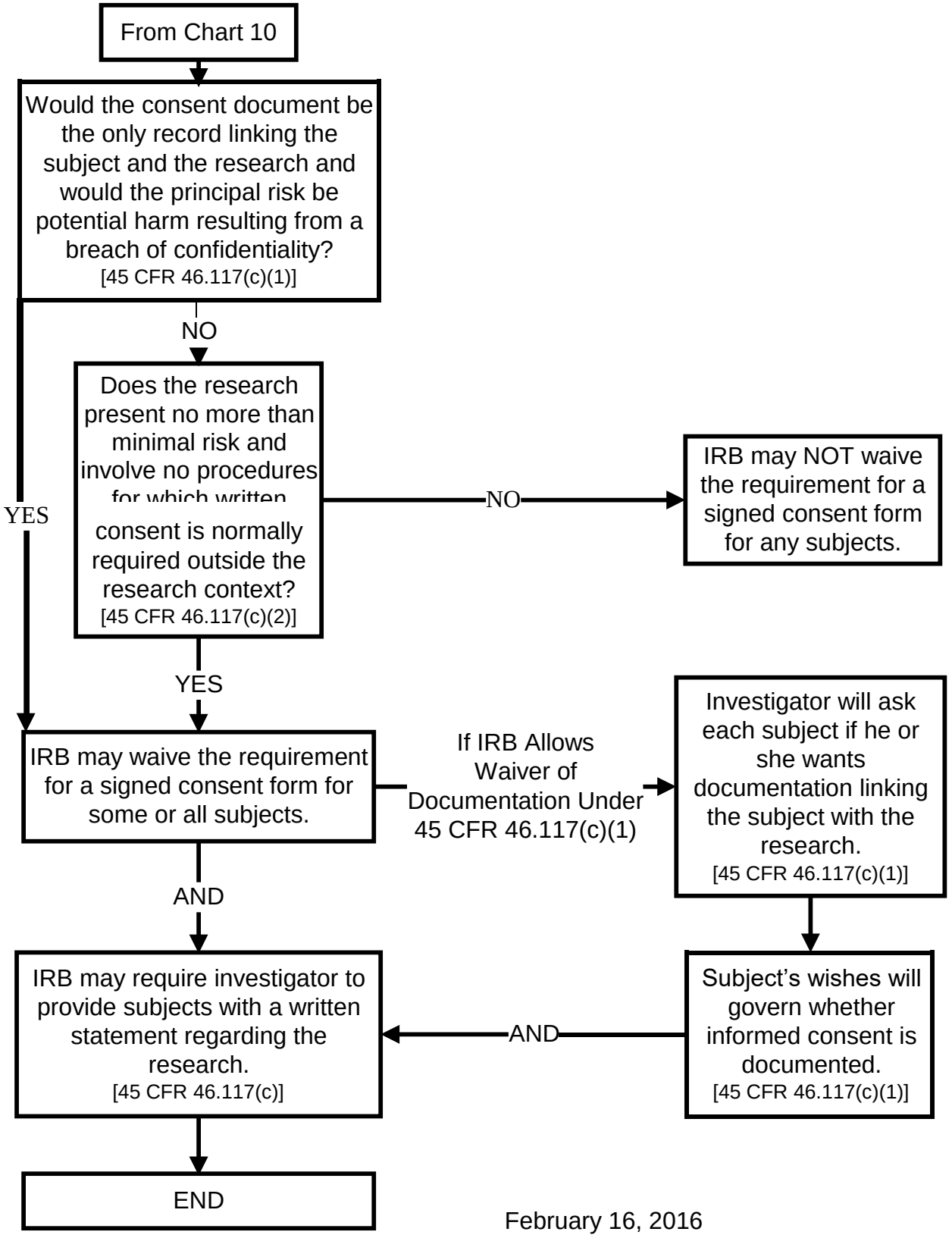
Chart 11: May Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?



February 16, 2016

Code of Federal Regulations

TITLE 45
PUBLIC WELFARE

Department of Health and Human Services

PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised January 15, 2009
Effective July 14, 2009

SUBPART A—
Basic HHS Policy for Protection of Human Research Subjects

Sec.

SUBPART B—
Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Sec.

SUBPART C— Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Sec.

SUBPART D— Additional Protections for Children Involved as Subjects in Research

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 289 (a).

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SUBPART E — Registration of Institutional Review Boards

Sec.

Editorial Note: The Department of Health and Human Services issued a notice of waiver regarding the requirements set forth in part 46, relating to protection of human subjects, as they pertain to demonstration projects, approved under section 1115 of the Social Security Act, which test the use of cost-sharing, such as deductibles, copayment and coinsurance, in the Medicaid program. For further information see 47 FR 9208, Mar. 4, 1982.

SUBPART A
Basic HHS Policy for Protection of Human Research Subjects

Authority: 5 U.S.C. 301; 42 U.S.C. 289; 42 U.S.C. 300v-1(b).

Source: 56 FR 28012, 28022, June 18, 1991, unless otherwise noted.

§46.101 To what does this policy apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §46.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §46.102(e) must be reviewed and approved, in compliance with §46.101, §46.102, and §46.107 through §46.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:

(i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:(i) Public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.[1]

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.102 Definitions.

(a) *Department or agency head* means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) *Institution* means any public or private entity or agency (including federal, state, and other agencies).

(c) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

(e) *Research subject to regulation*, and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context

in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means 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.

(i) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

[1]Institutions with HHS-approved assurances on file will abide by provisions of Title 45 CFR part 46 subparts A-D. Some of the other departments and agencies have incorporated all provisions of Title 45 CFR part 46 into their policies and procedures as well. However, the exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners, subpart C. The exemption at 45 CFR 46.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, subpart D, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

§46.103 Assuring compliance with this policy -- research conducted or supported by any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1)A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to Federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §46.101(b) or (i).

(2)Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3)A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with §46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Human Research Protections, HHS, or any successor office.

(4)Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5)Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §46.101(b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991; 56 FR 29756, June 28, 1991, as amended at 70 FR 36328, June 23, 2005]

§§46.104--46.106 [Reserved]

§46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB

§46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §46.103(b)(4) and, to the extent required by, §46.103(b)(5).

(b) Except when an expedited review procedure is used (see §46.110), review proposed 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. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with §46.116. The IRB may require that information, in addition to that specifically mentioned in §46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b) 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 and found by the reviewer(s) to involve no more than minimal risk,

(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 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. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in §46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.111 Criteria for IRB approval of research.

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

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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

§46.112 Review by institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §46.103(b)(4) and §46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

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[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, 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.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

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

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

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

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

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

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

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

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

1) The research involves no more than minimal risk to the subjects;

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

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

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

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.117 Documentation of informed consent.

(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) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies 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 opportunity to read it 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 a 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 short form.

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

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

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

(Approved by the Office of Management and Budget under Control Number 0990-0260.)

[56 FR 28012, 28022, June 18, 1991, as amended at 70 FR 36328, June 23, 2005]

§46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §46.101(b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§46.119 Research undertaken without the intention of involving human subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the department or agency, and final approval given to the proposed change by the department or agency.

§46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§46.121 [Reserved]

§46.122 Use of Federal funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§46.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§46.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

Subpart B

Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research

Source: 66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.

(b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.

(c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.

(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions.

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.

(c) Fetus means the product of conception from implantation until delivery.

(d) Neonate means a newborn.

(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.

(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

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

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

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

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

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

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

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

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

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

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

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

§46.205 Research involving neonates.

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

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

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

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

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

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

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

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

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

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

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

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

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

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

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

(a) The IRB finds that the research presents

a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Subpart C

Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FR 53655, Nov. 16, 1978, unless otherwise noted.

§46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health and Human Services involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§46.303 Definitions.

As used in this subpart:

(a) *Secretary* means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) *DHHS* means the Department of Health and Human Services.

(c) *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) *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.

§46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in §46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) 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.

(b) 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 reviewed by more than one Board only one Board need satisfy this requirement.

[43 FR 53655, Nov. 16, 1978, as amended at 46 FR 8366, Jan. 26, 1981]

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(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 under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

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

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secre-

tary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:

(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.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

Subpart D

Additional Protections for Children Involved as Subjects in Research

Source: 48 FR 9818, March 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (i) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101 (b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101 of subpart A are applicable to this subpart.

[48 FR 9818, Mar.8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991.]

§46.402 Definitions.

The definitions in §46.102 of subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) *Permission* means the agreement of parent (s) or guardian to the participation of their child or ward in research.

(d) *Parent* means a child's biological or adoptive parent.

(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if 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.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that 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; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 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.

HHS will conduct or fund research in which the IRB finds that 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 assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements 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 §46.404, §46.405, or §46.406, 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;

(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 their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

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

(b) 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. 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, or not reasonably available, or when 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.

§46.409 Wards.

(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.

Subpart E

Registration of Institutional Review Boards

Source: 74 FR 2399, January 15, 2009, unless otherwise noted.

§46.501 What IRBs must be registered?

Each IRB that is designated by an institution under an assurance of compliance approved for federalwide use by the Office for Human Research Protections (OHRP) under §46.103(a) and that reviews research involving human subjects conducted or supported by the Department of Health and Human Services (HHS) must be registered with HHS. An individual authorized to act on behalf of the institution or organization operating the IRB must submit the registration information.

§46.502 What information must be provided when registering an IRB?

The following information must be provided to HHS when registering an IRB:

(a) The name, mailing address, and street address (if different from the mailing address) of the institution or organization operating the IRB(s); and the name, mailing address, phone number, facsimile number, and electronic mail address of the senior officer or head official of that institution or organization who is responsible for overseeing activities performed by the IRB.

(b) The name, mailing address, phone number, facsimile number, and electronic mail address of the contact person providing the registration information.

(c) The name, if any, assigned to the IRB by the institution or organization, and the IRB's mailing address, street address (if different from the mailing address), phone number, facsimile number, and electronic mail address.

(d) The name, phone number, and electronic mail address of the IRB chairperson.

(e)(1) The approximate numbers of:

(i) All active protocols; and

(ii) Active protocols conducted or supported by HHS.

(2) For purpose of this regulation, an ``active protocol'' is any protocol for which the IRB conducted an initial review or a continuing review at a convened meeting or under an expedited review procedure during the preceding twelve months.

(f) The approximate number of full-time equivalent positions devoted to the IRB's administrative activities.

§46.503 When must an IRB be registered?

An IRB must be registered before it can be designated under an assurance approved for federalwide use by OHRP under §46.103(a).

IRB registration becomes effective when reviewed and accepted by OHRP.

The registration will be effective for 3 years.

§46.504 How must an IRB be registered?

Each IRB must be registered electronically through http://ohrp.cit.nih.gov/efile unless an institution or organization lacks the ability to register its IRB(s) electronically. If an institution or organization lacks the ability to register an IRB electronically, it must send its IRB registration information in writing to OHRP.

§46.505 When must IRB registration information be renewed or updated?

(a) Each IRB must renew its registration every 3 years.

(b) The registration information for an IRB must be updated within 90 days after changes occur regarding the contact person who provided the IRB registration information or the IRB chairperson. The updated registration information must be submitted in accordance with §46.504.

(c) Any renewal or update that is submitted to, and accepted by, OHRP begins a new 3-year effective period.

(d) An institution's or organization's decision to disband a registered IRB which it is operating also must be reported to OHRP in writing within 30 days after permanent cessation of the IRB's review of HHS-conducted or -supported research.

For the reasons set forth in this preamble, the Federal Policy for the Protection of Human Subjects is amended.

Text of the Final Common Rule

The text of the final common rule appears below:

1. Part/subpart ____ is amended/revised/added to read as follows:

PART ____—PROTECTION OF HUMAN SUBJECTS

§ ____.101 To what does this policy apply?

(a) Except as detailed in § ____.104, this policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States. Institutions that are engaged in research described in this paragraph and institutional review boards (IRBs) reviewing research that is subject to this policy must comply with this policy.

(b) [Reserved]

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy and this judgment shall be exercised consistent with the ethical principles of the Belmont Report.[62]

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the Federal department or agency but not otherwise covered by this policy comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations that provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations that may otherwise be applicable and that provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the **Federal Register** or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy, provided the alternative procedures to be followed are consistent with the principles of the Belmont Report.[63] Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, or to the equivalent office within the appropriate Federal department or agency, and shall also publish them in the **Federal Register** or in such other manner as provided in department or agency procedures. The waiver notice must include a statement that identifies the conditions under which the waiver will be applied and a justification as to why the waiver is appropriate for the research, including how the decision is consistent with the principles of the Belmont Report.

(j) Federal guidance on the requirements of this policy shall be issued only after consultation, for the purpose of harmonization (to the extent appropriate), with other Federal departments and agencies that have adopted this policy, unless such consultation is not feasible.

(k) [Reserved]

(l) Compliance dates and transition provisions:

(1) For purposes of this section, the *pre-2018 Requirements* means this subpart as published in the 2016 edition of the Code of Federal Regulations.

(2) For purposes of this section, the *2018 Requirements* means the Federal Policy for the Protection of Human Subjects requirements contained in this subpart. The compliance date for § ____.114(b) (cooperative research) of the 2018 Requirements is January 20, 2020.

(3) Research initially approved by an IRB, for which such review was waived pursuant to § ____.101(i), or for which a determination was made that the research was exempt before January 19, 2018, shall comply with the pre-2018 Requirements, except that an institution engaged in such research on or after January 19, 2018, may instead comply with the 2018 Requirements if the institution determines that such ongoing research will comply with the 2018 Requirements and an IRB documents such determination.

(4) Research initially approved by an IRB, for which such review was waived pursuant to § ____.101(i), or for which a

[62] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.– Belmont Report. Washington, DC: U.S. Department of Health and Human Services. 1979.

[63] *Id.*

determination was made that the research was exempt on or after January 19, 2018, shall comply with the 2018 Requirements.

(m) Severability: Any provision of this part held to be invalid or unenforceable by its terms, or as applied to any person or circumstance, shall be construed so as to continue to give maximum effect to the provision permitted by law, unless such holding shall be one of utter invalidity or unenforceability, in which event the provision shall be severable from this part and shall not affect the remainder thereof or the application of the provision to other persons not similarly situated or to other dissimilar circumstances.

§ ____.102 Definitions for purposes of this policy.

(a) *Certification* means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

(b) *Clinical trial* means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

(c) *Department or agency head* means the head of any Federal department or agency, for example, the Secretary of HHS, and any other officer or employee of any Federal department or agency to whom the authority provided by these regulations to the department or agency head has been delegated.

(d) *Federal department or agency* refers to a federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (*e.g.,* the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency).

(e)(1) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

(2) *Intervention* includes both physical procedures by which information or biospecimens are gathered (*e.g.,* venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

(3) *Interaction* includes communication or interpersonal contact between investigator and subject.

(4) *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.,* a medical record).

(5) *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

(6) *An identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

(7) Federal departments or agencies implementing this policy shall:

(i) Upon consultation with appropriate experts (including experts in data matching and re-identification), reexamine the meaning of "identifiable private information," as defined in paragraph (e)(5) of this section, and "identifiable biospecimen," as defined in paragraph (e)(6) of this section. This reexamination shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. If appropriate and permitted by law, such Federal departments and agencies may alter the interpretation of these terms, including through the use of guidance.

(ii) Upon consultation with appropriate experts, assess whether there are analytic technologies or techniques that should be considered by investigators to generate "identifiable private information," as defined in paragraph (e)(5) of this section, or an "identifiable biospecimen," as defined in paragraph (e)(6) of this section. This assessment shall take place within 1 year and regularly thereafter (at least every 4 years). This process will be conducted by collaboration among the Federal departments and agencies implementing this policy. Any such technologies or techniques will be included on a list of technologies or techniques that produce identifiable private information or identifiable biospecimens. This list will be published in the **Federal Register** after notice and an opportunity for public comment. The Secretary, HHS, shall maintain the list on a publicly accessible Web site.

(f) *Institution* means any public or private entity, or department or agency (including federal, state, and other agencies).

(g) *IRB* means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) *IRB approval* means 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.

(i) *Legally authorized representative* means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

(j) *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(k) *Public health authority* means an agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

(l) *Research* means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and

service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:

(1) Scholarly and journalistic activities (*e.g.*, oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

(m) *Written*, or *in writing*, for purposes of this part, refers to writing on a tangible medium (*e.g.*, paper) or in an electronic format.

§ ____.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.

(a) Each institution engaged in research that is covered by this policy, with the exception of research eligible for exemption under § ____.104, and that is conducted or supported by a Federal department or agency, shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements of this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Human Research Protections, HHS, or any successor office, and approved for Federal-wide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Human Research Protections, HHS, or any successor office. Federal departments and agencies will conduct or support research covered by this policy only if the institution has provided an assurance that it will comply with the requirements of this policy, as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB (if such certification is required by § ____.103(d)).

(b) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(c) The department or agency head may limit the period during which any assurance shall remain effective or otherwise condition or restrict the assurance.

(d) Certification is required when the research is supported by a Federal department or agency and not otherwise waived under § ____.101(i) or exempted under § ____.104. For such research, institutions shall certify that each proposed research study covered by the assurance and this section has been reviewed and approved by the IRB. Such certification must be submitted as prescribed by the Federal department or agency component supporting the research. Under no condition shall research covered by this section be initiated prior to receipt of the certification that the research has been reviewed and approved by the IRB.

(e) For nonexempt research involving human subjects covered by this policy (or exempt research for which limited IRB review takes place pursuant to § ____.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8)) that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall document the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (*e.g.*, in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol).

(Approved by the Office of Management and Budget under Control Number 0990–0260)

§ ____.104 Exempt research.

(a) Unless otherwise required by law or by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the categories in paragraph (d) of this section are exempt from the requirements of this policy, except that such activities must comply with the requirements of this section and as specified in each category.

(b) Use of the exemption categories for research subject to the requirements of subparts B, C, and D: Application of the exemption categories to research subject to the requirements of 45 CFR part 46, subparts B, C, and D, is as follows:

(1) *Subpart B.* Each of the exemptions at this section may be applied to research subject to subpart B if the conditions of the exemption are met.

(2) *Subpart C.* The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

(3) *Subpart D.* The exemptions at paragraphs (d)(1), (4), (5), (6), (7), and (8) of this section may be applied to research subject to subpart D if the conditions of the exemption are met. Paragraphs (d)(2)(i) and (ii) of this section only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (d)(2)(iii) of this section may not be applied to research subject to subpart D.

(c) [Reserved.]

(d) Except as described in paragraph (a) of this section, the following categories of human subjects research are exempt from this policy:

(1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques,

curricula, or classroom management methods.

(2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § ____.111(a)(7).

(3)(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § ____.111(a)(7).

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*

(5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(ii) [Reserved]

(6) Taste and food quality evaluation and consumer acceptance studies:

(i) If wholesome foods without additives are consumed, or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the

determinations required by § ____.111(a)(8).

(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with § ____.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with § ____.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by § ____.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

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§ ____.105 [Reserved.]

§ ____.106 [Reserved]

§ ____.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members (professional competence), and the diversity of its members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects.

(b) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(c) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(d) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(e) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ ____.108 IRB functions and operations.

(a) In order to fulfill the requirements of this policy each IRB shall:

(1) Have access to meeting space and sufficient staff to support the IRB's review and recordkeeping duties;

(2) Prepare and maintain a current list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications or licenses sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution, for example, full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant;

(3) Establish and follow written procedures for:

(i) Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(ii) Determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(iii) Ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject.

(4) Establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections, HHS, or any successor office, or the equivalent office within the appropriate Federal department or agency of

(i) Any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and

(ii) Any suspension or termination of IRB approval.

(b) Except when an expedited review procedure is used (as described in § ____.110), an IRB must review proposed 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. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

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§ ____.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy, including exempt research activities under § ____.104 for which limited IRB review is a condition of exemption (under § ____.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8)).

(b) An IRB shall require that information given to subjects (or legally authorized representatives, when appropriate) as part of informed consent is in accordance with § ____.116. The IRB may require that information, in addition to that specifically mentioned in § ____.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § ____.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB

approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk, not less than once per year, except as described in § ____.109(f).

(f)(1) Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances:

(i) Research eligible for expedited review in accordance with § ____.110;

(ii) Research reviewed by the IRB in accordance with the limited IRB review described in § ____.104(d)(2)(iii), (d)(3)(i)(C), or (d)(7) or (8);

(iii) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

(A) Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

(B) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

(2) [Reserved.]

(g) An IRB shall have authority to observe or have a third party observe the consent process and the research.

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§ ____.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary of HHS has established, and published as a Notice in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it, as appropriate, after consultation with other federal departments and agencies and after publication in the **Federal Register** for public comment. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office.

(b)(1) An IRB may use the expedited review procedure to review the following:

(i) Some or all of the research appearing on the list described in paragraph (a) of this section, unless the reviewer determines that the study involves more than minimal risk;

(ii) Minor changes in previously approved research during the period for which approval is authorized; or

(iii) Research for which limited IRB review is a condition of exemption under § ____.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

(2) 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 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. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in § ____.108(b).

(c) Each IRB that uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals that have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§ ____.111 Criteria for IRB approval of research.

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

(1) Risks to subjects are minimized:

(i) By using procedures that are consistent with sound research design and that 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 (*e.g.*, 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. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, 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, § ____.116.

(5) Informed consent will be appropriately documented or appropriately waived in accordance with § ____.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.

(i) The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

(ii) [Reserved.]

(8) For purposes of conducting the limited IRB review required by § ____.104(d)(7)), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations:

(i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of § ____.116(a)(1)–(4), (a)(6), and (d);

(ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with § ____.117; and

(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ ____.112 Review by Institution

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ ____.113 Suspension or Termination of IRB Approval of Research

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

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§ ____.114 Cooperative Research

(a) Cooperative research projects are those projects covered by this policy that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.

(b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(2) The following research is not subject to this provision:

(i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or

(ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

§ ____.115 IRB Records

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent forms, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in § ____.109(f)(1).

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in § ____.108(a)(2).

(6) Written procedures for the IRB in the same detail as described in § ____.108(a)(3) and (4).

(7) Statements of significant new findings provided to subjects, as required by § ____.116(c)(5).

(8) The rationale for an expedited reviewer's determination under § ____.110(b)(1)(i) that research appearing on the expedited review list described in § ____.110(a) is more than minimal risk.

(9) Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this policy, as described in § ____.103(e).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research that is conducted shall be retained for at least 3 years after completion of the research. The institution or IRB may maintain the records in printed form, or electronically. All records shall be accessible for inspection and copying by authorized representatives of the Federal department or agency at reasonable times and in a reasonable manner.

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§ ____.116 General Requirements for Informed Consent

(a) *General.* General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens. Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials is described in paragraph (e) of this section. General waiver or alteration of informed consent is described in paragraph (f) of this section. Except as provided elsewhere in this policy:

(1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.

(2) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.

(3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.

(4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

(5) Except for broad consent obtained in accordance with paragraph (d) of this section:

(i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

(ii) Informed consent as a whole must present information in sufficient detail

relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

(6) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

(b) *Basic elements of informed consent.* Except as provided in paragraph (d), (e), or (f) of this section, in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:

(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 that 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 that may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

(c) *Additional elements of informed consent.* Except as provided in paragraph (d), (e), or (f) of this section, one or more of the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative'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 that may relate to the subject's willingness to continue participation will be provided to the subject;

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

(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (*i.e.*, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

(d) *Elements of broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.* Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) is permitted as an alternative to the informed consent requirements in paragraphs (b) and (c) of this section. If the subject or the legally authorized representative is asked to provide broad consent, the following shall be provided to each subject or the subject's legally authorized representative:

(1) The information required in paragraphs (b)(2), (b)(3), (b)(5), and (b)(8) and, when appropriate, (c)(7) and (9) of this section;

(2) A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;

(3) A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;

(4) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);

(5) Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;

(6) Unless it is known that clinically relevant research results, including individual research results, will be

disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

(7) An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

(e) *Waiver or alteration of consent in research involving public benefit and service programs conducted by or subject to the approval of state or local officials*—(1) *Waiver.* An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (e)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) *Alteration.* An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (e)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) *Requirements for waiver and alteration.* In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

(i) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(A) Public benefit or service programs;

(B) Procedures for obtaining benefits or services under those programs;

(C) Possible changes in or alternatives to those programs or procedures; or

(D) Possible changes in methods or levels of payment for benefits or services under those programs; and

(ii) The research could not practicably be carried out without the waiver or alteration.

(f) *General waiver or alteration of consent*—(1) *Waiver.* An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section, provided the IRB satisfies the requirements of paragraph (f)(3) of this section. If an individual was asked to provide broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens in accordance with the requirements at paragraph (d) of this section, and refused to consent, an IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens.

(2) *Alteration.* An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (f)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.

(3) *Requirements for waiver and alteration.* In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

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

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

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;

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

(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

(g) *Screening, recruiting, or determining eligibility.* An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

(1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or

(2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

(h) *Posting of clinical trial consent form.* (1) For each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms.

(2) If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (*e.g.* confidential commercial information), such Federal department or agency may permit or require redactions to the information posted.

(3) The informed consent form must be posted on the Federal Web site after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

(i) *Preemption.* The informed consent requirements in this policy are not intended to preempt any applicable Federal, state, or local laws (including tribal laws passed by the official governing body of an American Indian or Alaska Native tribe) that require additional information to be disclosed in order for informed consent to be legally effective.

(j) *Emergency medical care.* Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, state, or local law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe).

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§ ____.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written informed consent form approved by the IRB and signed (including in an electronic format) by the subject or the subject's legally authorized representative. A written copy shall be given to the person signing the informed consent form.

(b) Except as provided in paragraph (c) of this section, the informed consent form may be either of the following:

(1) A written informed consent form that meets the requirements of § ____.116. The investigator shall give either the subject or the subject's legally authorized representative adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative.

(2) A short form written informed consent form stating that the elements of informed consent required by § ____.116 have been presented orally to the subject or the subject's legally authorized representative, and that the key information required by § ____.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.

(c)(1) An IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects if it finds any of the following:

(i) That the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or legally authorized representative) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern;

(ii) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context; or

(iii) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

(2) In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

(Approved by the Office of Management and Budget under Control Number 0990–0260)

§ ____.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to Federal departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. Except for research waived under § ____.101(i) or exempted under § ____.104, no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the Federal department or agency component supporting the research.

§ ____.119 Research undertaken without the intention of involving human subjects.

Except for research waived under § ____.101(i) or exempted under § ____.104, in the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted by the institution to the Federal department or agency component supporting the research, and final approval given to the proposed change by the Federal department or agency component.

§ ____.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the Federal department or agency through such officers and employees of the Federal department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ ____.121 [Reserved]

§ ____.122 Use of Federal funds.

Federal funds administered by a Federal department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§ ____.123 Early termination of research support: Evaluation of applications and proposals.

(a) The department or agency head may require that Federal department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has/have directed the scientific and technical aspects of an activity has/have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§ ____.124 Conditions.

With respect to any research project or any class of research projects the department or agency head of either the conducting or the supporting Federal department or agency may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head

additional conditions are necessary for the protection of human subjects.

Adoption of the Common Rules

The adoption of the common rules by the participating agencies, as modified by agency-specific text, is set forth below.

DEPARTMENT OF HOMELAND SECURITY

List of Subjects in 6 CFR Part 46

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Homeland Security adds 6 CFR part 46 as set forth at the end of the common preamble of this document.

PART 46—PROTECTION OF HUMAN SUBJECTS

Sec.
46.101 To what does this policy apply?
46.102 Definitions for purposes of this policy.
46.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
46.104 Exempt research.
46.105 [Reserved]
46.106 [Reserved]
46.107 IRB membership.
46.108 IRB functions and operations.
46.109 IRB review of research.
46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
46.111 Criteria for IRB approval of research.
46.112 Review by institution.
46.113 Suspension or termination of IRB approval of research.
46.114 Cooperative research.
46.115 IRB records.
46.116 General requirements for informed consent.
46.117 Documentation of informed consent.
46.118 Applications and proposals lacking definite plans for involvement of human subjects.
46.119 Research undertaken without the intention of involving human subjects.
46.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
46.121 [Reserved]
46.122 Use of Federal funds.
46.123 Early termination of research support: Evaluation of applications and proposals.
46.124 Conditions.

Authority: 5 U.S.C. 301; Pub. L. 107–296, sec. 102, 306(c); Pub. L. 108–458, sec. 8306.

Reginald Brothers,
Under Secretary for Science and Technology, DHS.

DEPARTMENT OF AGRICULTURE

List of Subjects in 7 CFR Part 1c

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Agriculture revises 7 CFR part 1c as set forth at the end of the common preamble of this document.

PART 1c—PROTECTION OF HUMAN SUBJECTS

Sec.
1c.101 To what does this policy apply?
1c.102 Definitions for purposes of this policy.
1c.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
1c.104 Exempt research.
1c.105 [Reserved]
1c.106 [Reserved]
1c.107 IRB membership.
1c.108 IRB functions and operations.
1c.109 IRB review of research.
1c.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
1c.111 Criteria for IRB approval of research.
1c.112 Review by institution.
1c.113 Suspension or termination of IRB approval of research.
1c.114 Cooperative research.
1c.115 IRB records.
1c.116 General requirements for informed consent.
1c.117 Documentation of informed consent.
1c.118 Applications and proposals lacking definite plans for involvement of human subjects.
1c.119 Research undertaken without the intention of involving human subjects.
1c.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
1c.121 [Reserved]
1c.122 Use of Federal funds.
1c.123 Early termination of research support: Evaluation of applications and proposals.
1c.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b).

Ann M. Bartuska,
Acting Under Secretary for Research, Education, and Economics, USDA.

DEPARTMENT OF ENERGY

List of Subjects in 10 CFR Part 745

10 CFR Part 745

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Energy revises 10 CFR part 745 as set forth at the end of the common preamble of this document.

PART 745—PROTECTION OF HUMAN SUBJECTS

Sec.
745.101 To what does this policy apply?
745.102 Definitions for purposes of this policy.
745.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
745.104 Exempt research.
745.105 [Reserved]
745.106 [Reserved]
745.107 IRB membership.
745.108 IRB functions and operations.
745.109 IRB review of research.
745.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
745.111 Criteria for IRB approval of research.
745.112 Review by institution.
745.113 Suspension or termination of IRB approval of research.
745.114 Cooperative research.
745.115 IRB records.
745.116 General requirements for informed consent.
745.117 Documentation of informed consent.
745.118 Applications and proposals lacking definite plans for involvement of human subjects.
745.119 Research undertaken without the intention of involving human subjects.
745.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
745.121 [Reserved]
745.122 Use of Federal funds.
745.123 Early termination of research support: Evaluation of applications and proposals.
745.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 7254; 42 U.S.C. 300v–1(b).

Elizabeth Sherwood-Randall,

Deputy Secretary of Energy.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

List of Subjects in 14 CFR Part 1230

14 CFR Part 1230

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the National Aeronautics and Space Administration revises 14 CFR part 1230 as set forth at the end of the common preamble of this document.

PART 1230—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301;42 U.S.C. 300v–1(b).

James D. Polk,

Chief Health and Medical Officer, NASA.

DEPARTMENT OF COMMERCE

List of Subjects in 15 CFR Part 27

15 CFR Part 27

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Commerce revises 15 CFR part 27 as set forth at the end of the common preamble of this document.

PART 27—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b).

James Hock,

Chief of Staff, Department of Commerce.

SOCIAL SECURITY ADMINISTRATION

List of Subjects in 20 CFR Part 431

20 CFR Part 431

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Social Security Administration adds 20 CFR part 431 as set forth at the end of the common preamble of this document.

PART 431—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

Carolyn W. Colvin,

Acting Commissioner of Social Security.

AGENCY FOR INTERNATIONAL DEVELOPMENT

List of Subjects in 22 CFR Part 225

22 CFR Part 225

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Agency for International Development revises 22 CFR part 225 as set forth at the end of the common preamble of this document.

PART 225—PROTECTION OF HUMAN SUBJECTS

Sec.

225.101 To what does this policy apply?
225.102 Definitions for purposes of this policy.
225.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
225.104 Exempt research.
225.105 [Reserved]
225.106 [Reserved]
225.107 IRB membership.
225.108 IRB functions and operations.
225.109 IRB review of research.
225.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
225.111 Criteria for IRB approval of research.
225.112 Review by institution.
225.113 Suspension or termination of IRB approval of research.
225.114 Cooperative research.
225.115 IRB records.
225.116 General requirements for informed consent.
225.117 Documentation of informed consent.
225.118 Applications and proposals lacking definite plans for involvement of human subjects.
225.119 Research undertaken without the intention of involving human subjects.
225.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
225.121 [Reserved]
225.122 Use of Federal funds.
225.123 Early termination of research support: Evaluation of applications and proposals.
225.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b), unless otherwise noted.

Irene Koek,

Acting Deputy Assistant Administrator for Global Health, U.S. Agency for International Development.

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

List of Subjects in 24 CFR Part 60

24 CFR Part 60

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Housing and Urban Development revises 24 CFR part 60 as set forth at the end of the common preamble of this document.

PART 60—PROTECTION OF HUMAN SUBJECTS

Sec.

60.101 To what does this policy apply?
60.102 Definitions for purposes of this policy.
60.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
60.104 Exempt research.
60.105 [Reserved]
60.106 [Reserved]
60.107 IRB membership.
60.108 IRB functions and operations.
60.109 IRB review of research.
60.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
60.111 Criteria for IRB approval of research.
60.112 Review by institution.
60.113 Suspension or termination of IRB approval of research.
60.114 Cooperative research.
60.115 IRB records.
60.116 General requirements for informed consent.
60.117 Documentation of informed consent.
60.118 Applications and proposals lacking definite plans for involvement of human subjects.
60.119 Research undertaken without the intention of involving human subjects.
60.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
60.121 [Reserved]
60.122 Use of Federal funds.
60.123 Early termination of research support: Evaluation of applications and proposals.
60.124 Conditions.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b) and 3535(d).

Katherine M. O'Regan,

Assistant Secretary for Policy Development and Research, Department of Housing and Urban Development.

DEPARTMENT OF LABOR

List of Subjects in 29 CFR Part 21

29 CFR Part 21

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Labor adds 29 CFR part 21 as set forth at the end of the common preamble of this document.

PART 21—PROTECTION OF HUMAN SUBJECTS

Sec.

21.101 To what does this policy apply?
21.102 Definitions for purposes of this policy.
21.103 Assuring compliance with this policy—research conducted or supported by any Federal department or agency.
21.104 Exempt research.
21.105 [Reserved]
21.106 [Reserved]
21.107 IRB membership.
21.108 IRB functions and operations.
21.109 IRB review of research.
21.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.
21.111 Criteria for IRB approval of research.
21.112 Review by institution.
21.113 Suspension or termination of IRB approval of research.
21.114 Cooperative research.
21.115 IRB records.
21.116 General requirements for informed consent.
21.117 Documentation of informed consent.
21.118 Applications and proposals lacking definite plans for involvement of human subjects.
21.119 Research undertaken without the intention of involving human subjects.
21.120 Evaluation and disposition of applications and proposals for research to be conducted or supported by a Federal department or agency.
21.121 [Reserved]
21.122 Use of Federal funds.
21.123 Early termination of research support: Evaluation of applications and proposals.
21.124 Conditions.

Authority: 5 U.S.C. 301; 29 U.S.C. 551.

Christopher P. Lu,

Deputy Secretary of Labor.

DEPARTMENT OF DEFENSE

List of Subjects in 32 CFR Part 219

32 CFR Part 219

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Defense revises 32 CFR part 219 as set forth at the end of the common preamble of this document.

PART 219—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b).

Stephen P. Welby,

Assistant Secretary of Defense (Research and Engineering).

DEPARTMENT OF EDUCATION

List of Subjects in 34 CFR Part 97

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Education amends 34 CFR part 97 as follows:

PART 97—PROTECTION OF HUMAN SUBJECTS

■ 1. The authority citation for part 97 continues to read as follows:

Authority: 5 U.S.C. 301; 20 U.S.C. 1221e–3, 3474; 42 U.S.C. 300v–1(b).

■ 2. Subpart A is revised as set forth at the end of the common preamble of this document.

Subpart A—Federal Policy for the Protection of Human Subjects (Basic ED Policy for Protection of Human Research Subjects)

Sec.

John B. King Jr.,

Secretary of Education.

DEPARTMENT OF VETERANS AFFAIRS

List of Subjects in 38 CFR Part 16

38 CFR Part 16

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Veterans Affairs revises 38 CFR part 16 as set forth at the end of the common preamble of this document.

PART 16—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 38 U.S.C. 501, 7331, 7334; 42 U.S.C. 300v–1(b).

Gina S. Farrisee,

Deputy Chief of Staff, U.S. Department of Veterans Affairs.

ENVIRONMENTAL PROTECTION AGENCY

List of Subjects in 40 CFR Part 26

40 CFR Part 26

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Environmental Protection Agency amends 40 CFR part 26 as follows:

PART 26—PROTECTION OF HUMAN SUBJECTS

■ 1. The authority citation for part 26 continues to read as follows:

Authority: 5 U.S.C. 301; 7 U.S.C. 136a(a) and 136w(a)(1); 21 U.S.C. 346a(e)(1)(C); sec. 201, Pub. L. 109–54, 119 Stat. 531; and 42 U.S.C. 300v–1(b).

■ 2. Subpart A is revised as set forth at the end of the common preamble of this document.

Subpart A—Basic EPA Policy for Protection of Subjects in Human Research Conducted or Supported by EPA

Sec.

A. Stanley Meiburg,

Acting Deputy Administrator, Environmental Protection Agency.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

List of Subjects in 45 CFR Part 46

45 CFR Part 46

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Health and Human Services amends 45 CFR part 46 as follows:

PART 46—PROTECTION OF HUMAN SUBJECTS

■ 1. The authority citation for part 46 is revised to read as follows:

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a); 42 U.S.C. 300v–1(b).

■ 2. Subpart A is revised as set forth at the end of the common preamble of this document.

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

Sec.

Sylvia M. Burwell,

Secretary, HHS.

NATIONAL SCIENCE FOUNDATION

List of Subjects in 45 CFR Part 690

45 CFR Part 690

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the National Science Foundation revises 45 CFR part 690 as set forth at the end of the common preamble of this document.

PART 690—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b).

Lawrence Rudolph,

General Counsel, National Science Foundation.

DEPARTMENT OF TRANSPORTATION

List of Subjects in 49 CFR Part 11

49 CFR Part 11

Human research subjects, Reporting and record-keeping requirements, Research.

■ For the reasons stated in the preamble, the Department of Transportation revises 49 CFR part 11 as set forth at the end of the common preamble of this document.

PART 11—PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v–1(b).

Anthony R. Foxx,

Secretary of Transportation.

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