



# Good Clinical Practice Resource Guide

Division of Microbiology and Infectious Diseases  
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The Division of Microbiology and Infectious Diseases (DMID), within the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institutes of Health (NIH) is pleased to provide this resource guide, containing selected Good Clinical Practice (GCP) regulations and guidelines for sites conducting DMID-supported clinical trials. As content is subject to change, every effort is made to ensure the most accurate and current regulations and guidance documents are included (see “Useful Internet Sites”).

GCP standards are well-established practices which apply to all aspects of a clinical trial; ethical and scientific study design including collecting, recording, reporting and maintaining accurate clinical trial data, and rigorous assurances for the protections of human subjects enrolled in clinical trials.

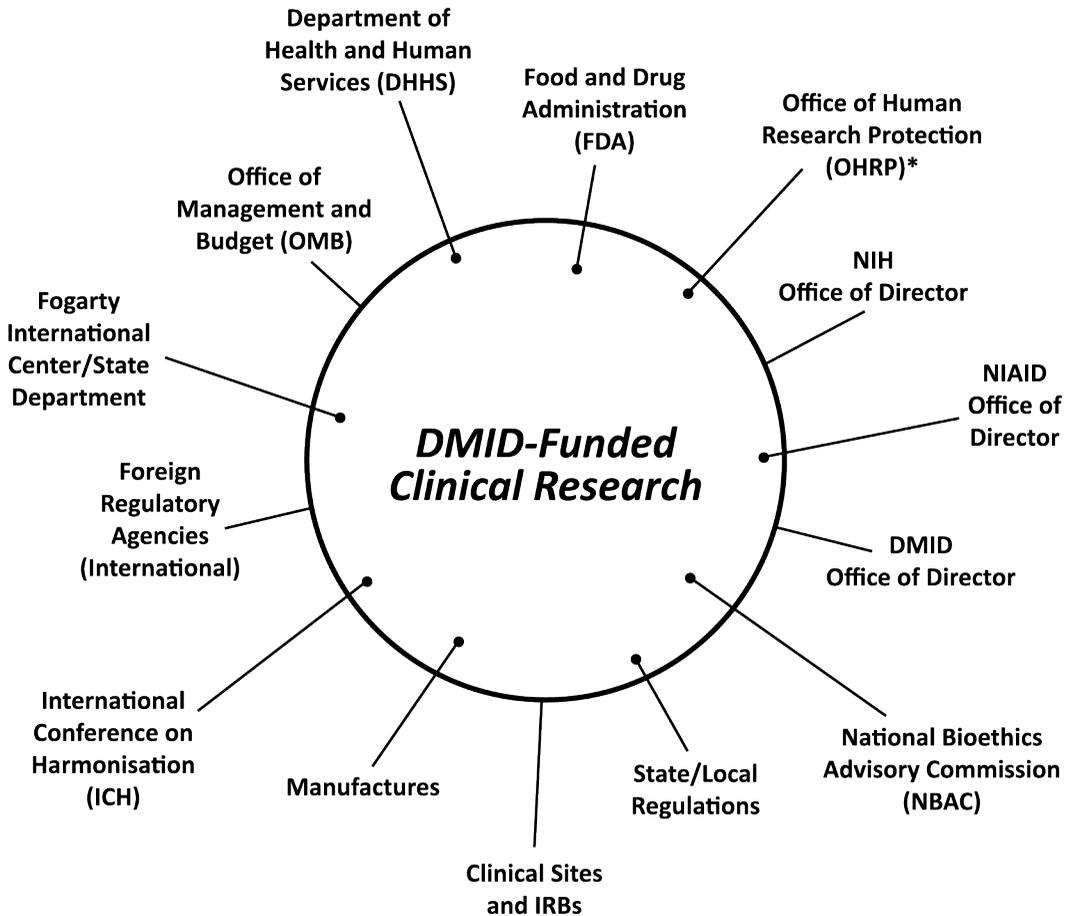
Where appropriate, special attention should be paid to state and local regulations, as well as non-U.S. sites. DMID requires adherence to human subjects protections regulations (45 CFR 46) and applicable GCP standards throughout the conduct and management of a clinical trial, including U.S. federal regulations for Investigational New Drug Application (IND) 21 CFR 312, and Investigational Device Exemption (IDE), 21 CFR 812, as appropriate.

Conducting DMID-supported clinical trials requires;

- Written approval by a Office of Human Research Protections (OHRP) - registered Institutional Review Board (IRB), in compliance with the requirements of 21 Code of Federal Regulations (CFR) 56 (Institutional Review Boards) and 45 CFR 46, (Protection of Human Subjects) prior to initiating any study-related procedures.
- Valid and documented informed consent from all subjects, or their Legally Authorized Representatives (LAR), prior to participation in any research activities, in accordance with the requirements of 21 CFR 50 and 45 CFR 46.
- Compliance with international, federal, state and local requirements, including 21 CFR 312 and 21 CFR 812, as applicable.
- Conformity with the International Conference on Harmonisation (ICH) E6 (R1) GCP Guidelines.
- Compliance with the policies and procedures of the DMID, NIAID, and NIH.
- Appropriate medical care and treatment of study subjects.
- Retention of adequate written documentation to demonstrate regulatory compliance with all research activities.
- Cooperation with sponsor, government or regulatory agency clinical site monitors, inspectors, and auditors.



# Organizations Impacting Clinical Research



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\* The responsibilities of the Office for Protection from Research Risks (OPRR), NIH, have been transferred to the Office for Human Research Protections (OHRP), DHHS (Federal Register [FR]), June 13, 2000). Documents published by OPRR are still valid. For current OHRP contacts, please see the OHRP web page. (<http://www.hhs.gov/ohrp/index.html>)



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# I. Human Subjects Protection

## Human Subject Regulations Decision Charts

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

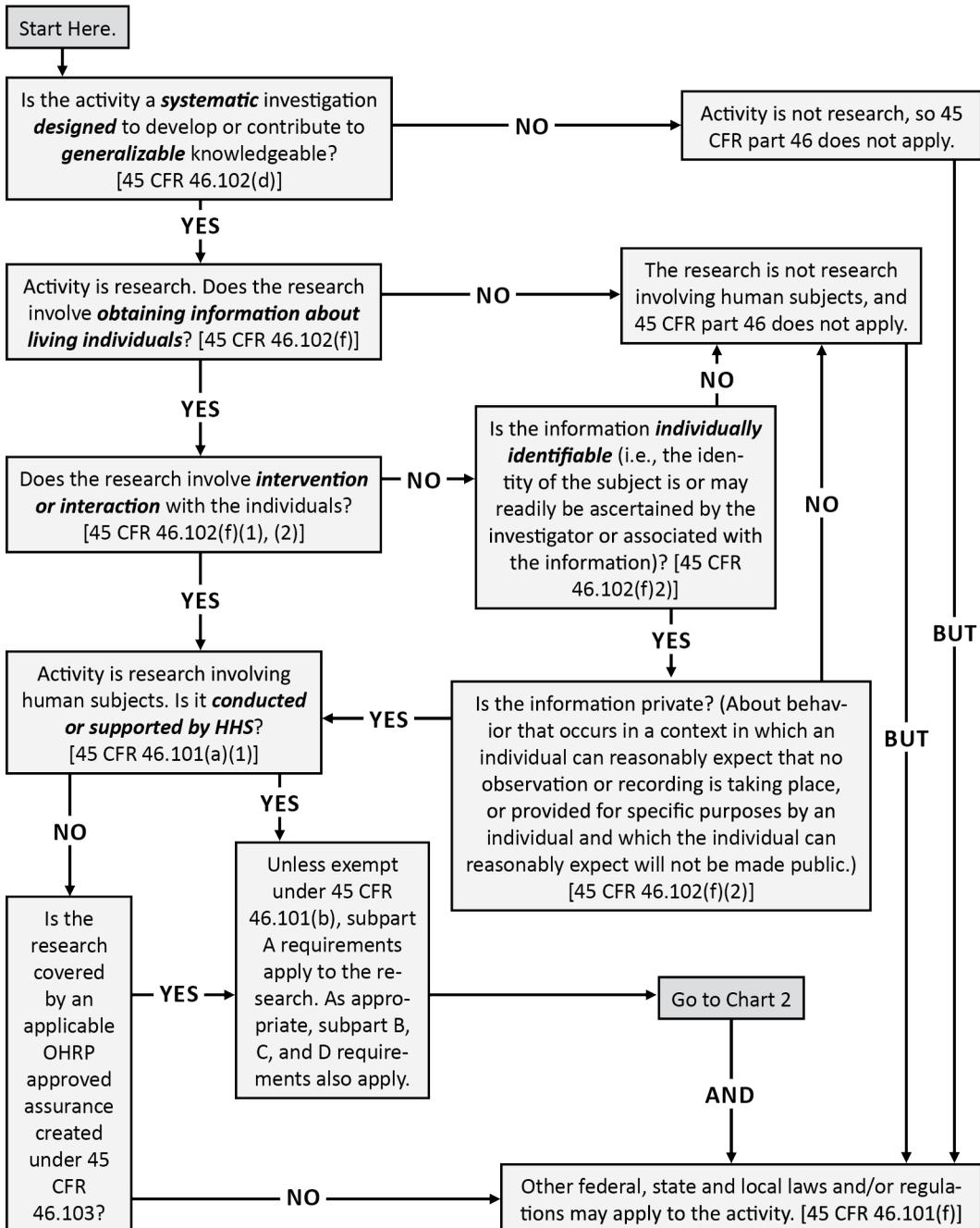
The charts are intended to assist IRBs, institutions, and investigators in their decision-making process and should not be used as substitutes for consulting the regulations. OHRP cautions that the full text of applicable regulatory provisions should be considered in making final decisions. These charts 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 Covered by 45 CFR part 46?**

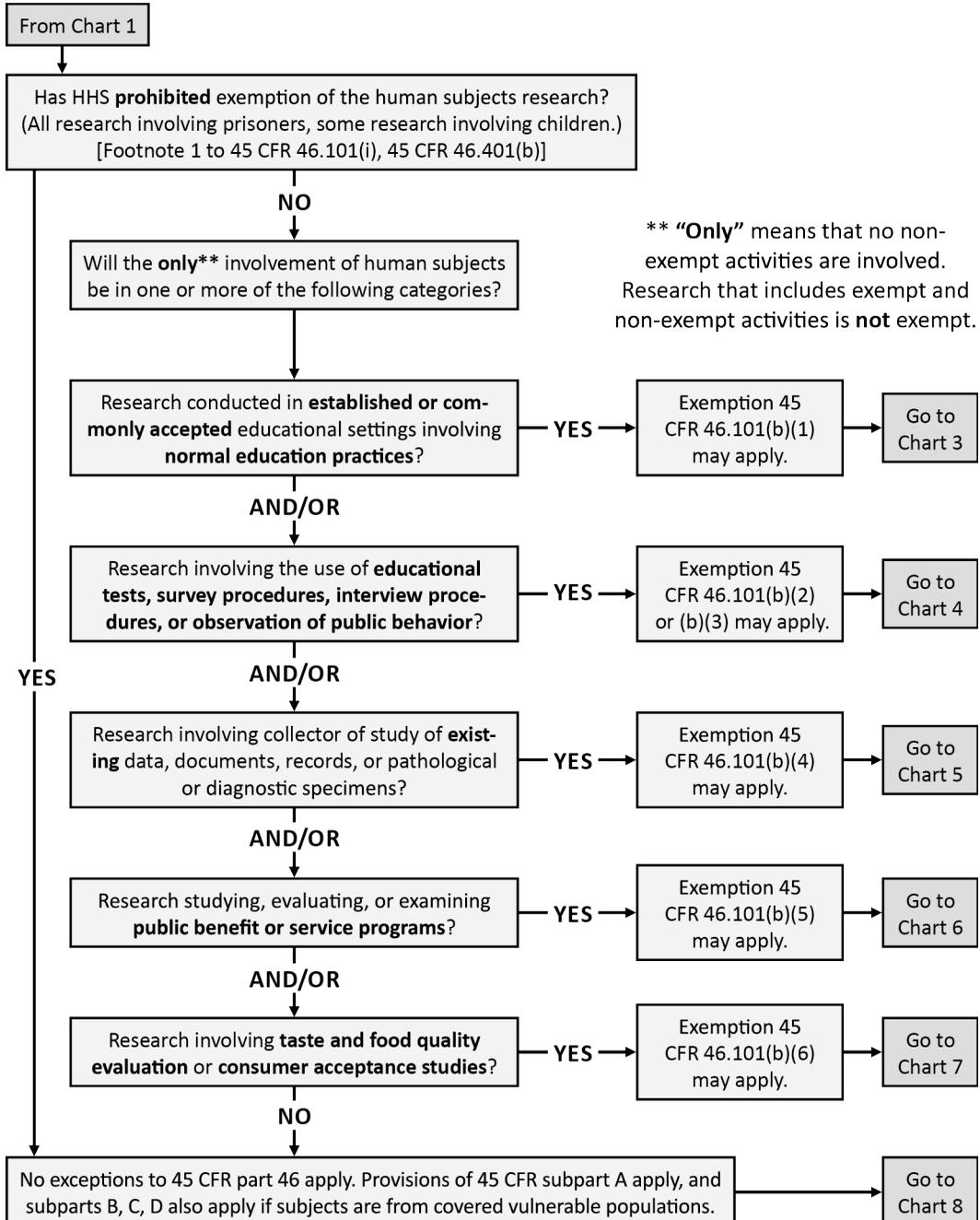
September 24, 2004



**CHART 2:**

**Is the Research Involving Human Subjects Eligible for Exemption Under 45 CFR 46.101(b)?**

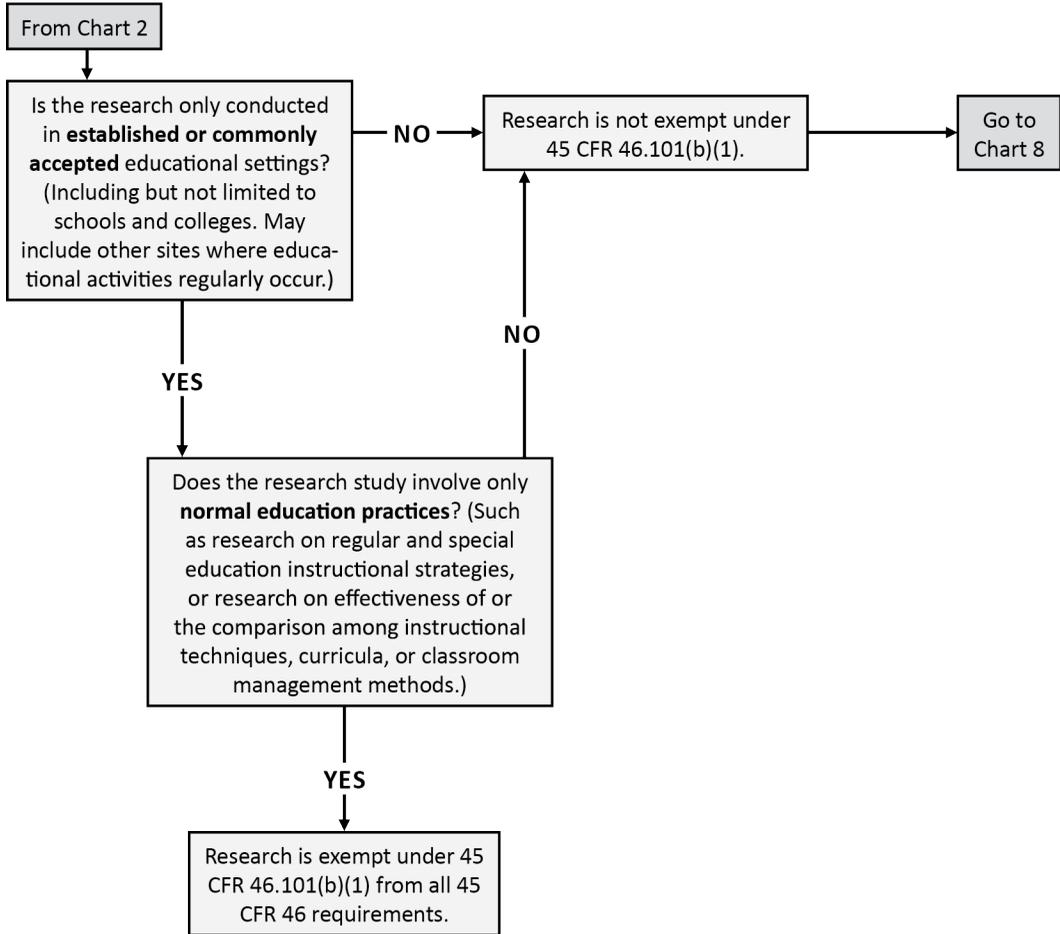
September 24, 2004



**CHART 3:**

**Does Exemption 45 CFR 46.101(b)(1)  
(for Educational Settings) Apply?**

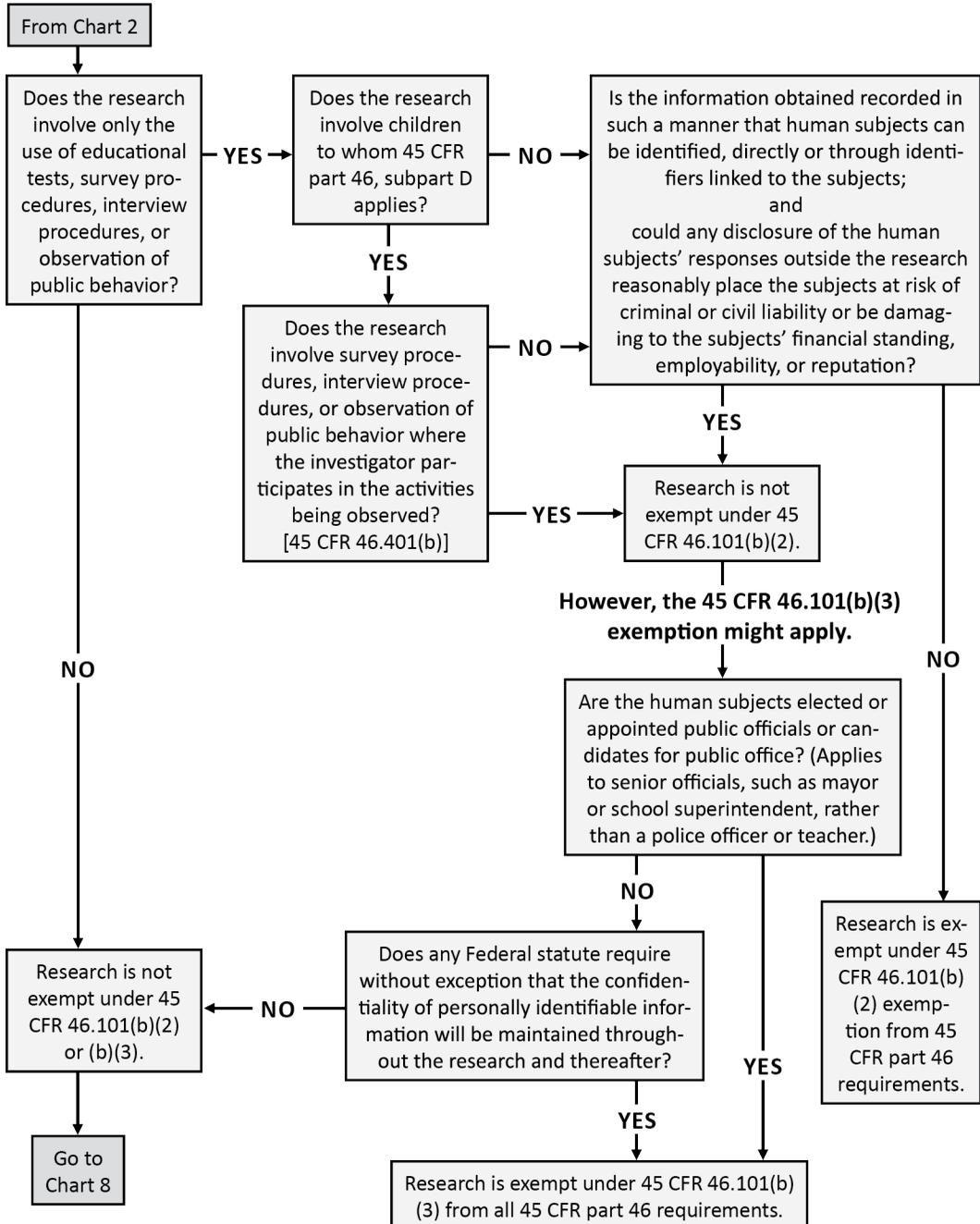
September 24, 2004



**CHART 4:**

**Does Exemption 45 CFR 46.101(b)(2) or (b)(3) (for Tests, Surveys, Interviews, Public Behavior Observation) Apply?**

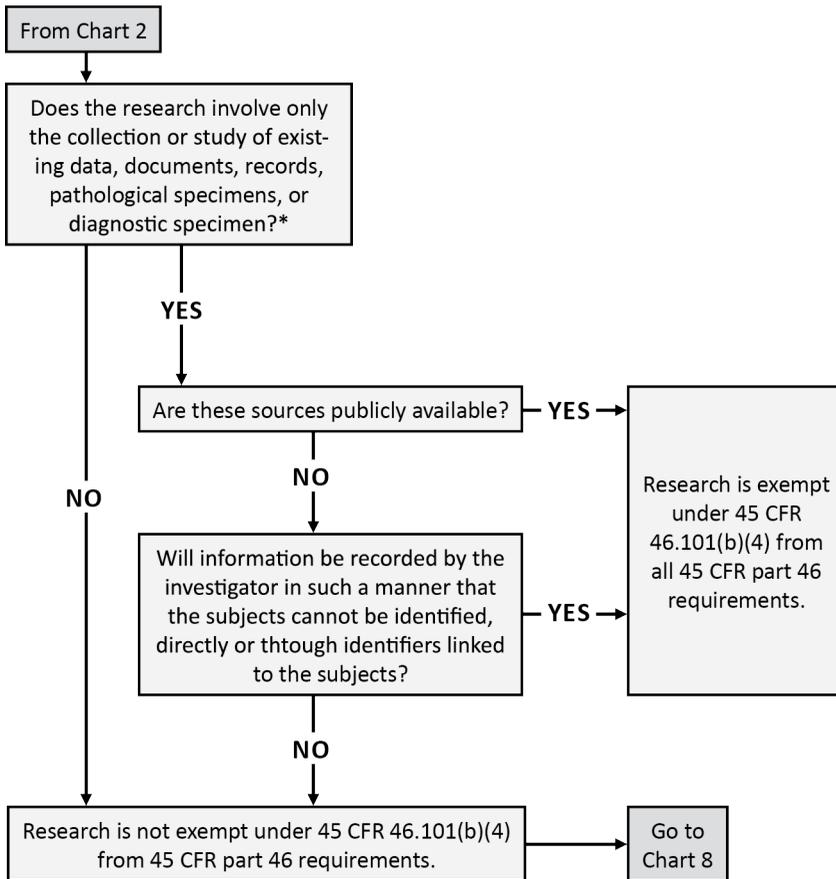
September 24, 2004



**CHART 5:**

**Does Exemption 45 CFR 46.101(b)(4)  
(for Existing Data Documentations and Specimens) Apply?**

September 24, 2004

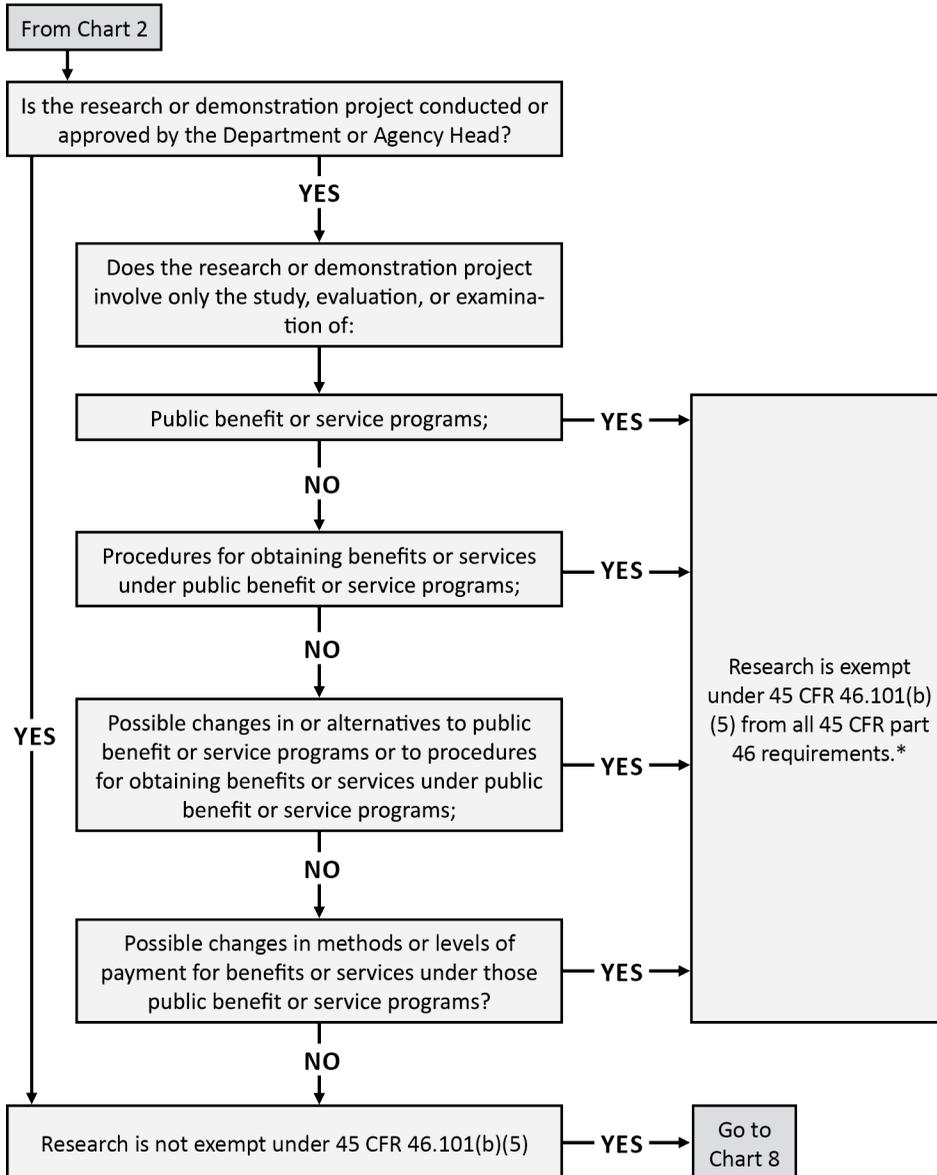


\* Note: See OHRP guidance on research use of stored data or tissues, on stem cells, and on coded data or specimens.

**CHART 6:**

**Does Exemption 45 CFR 46.101(b)(5)  
(for Public Benefit of Service Programs) Apply?**

September 24, 2004

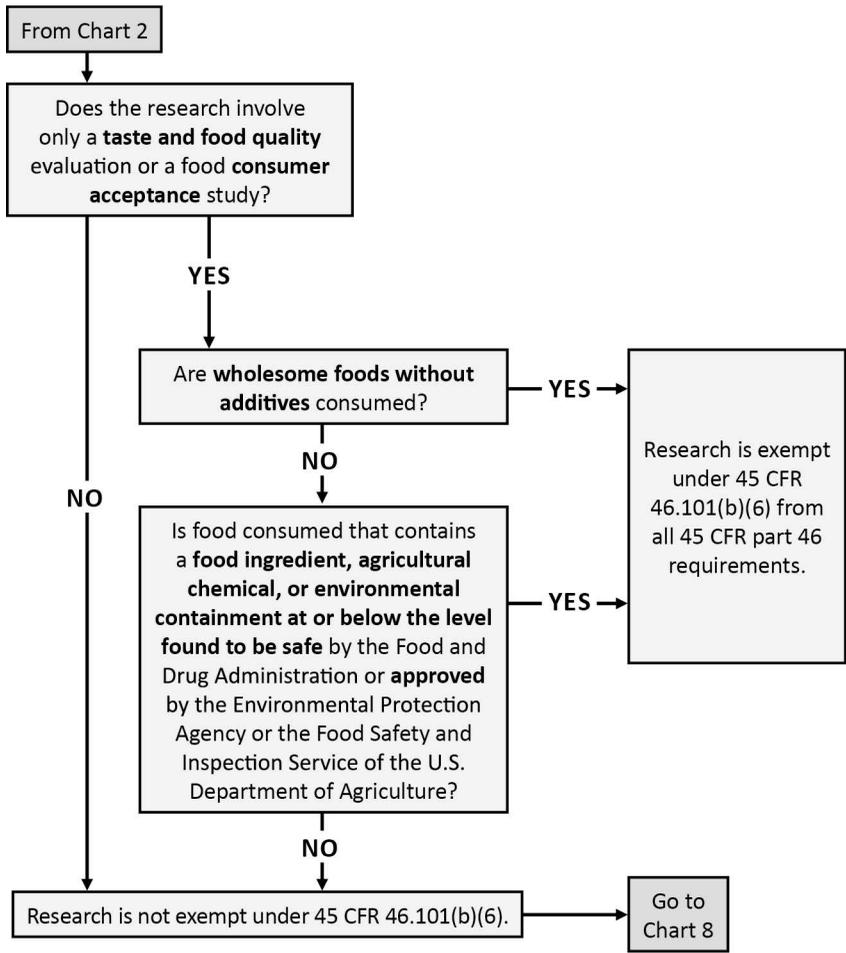


\* Note: See OHRP guidance on exceptions.

**CHART 7:**

**Does Exemption 45 CFR 46.101(b)(6)  
(for Food Taste and Acceptance Studies) Apply?**

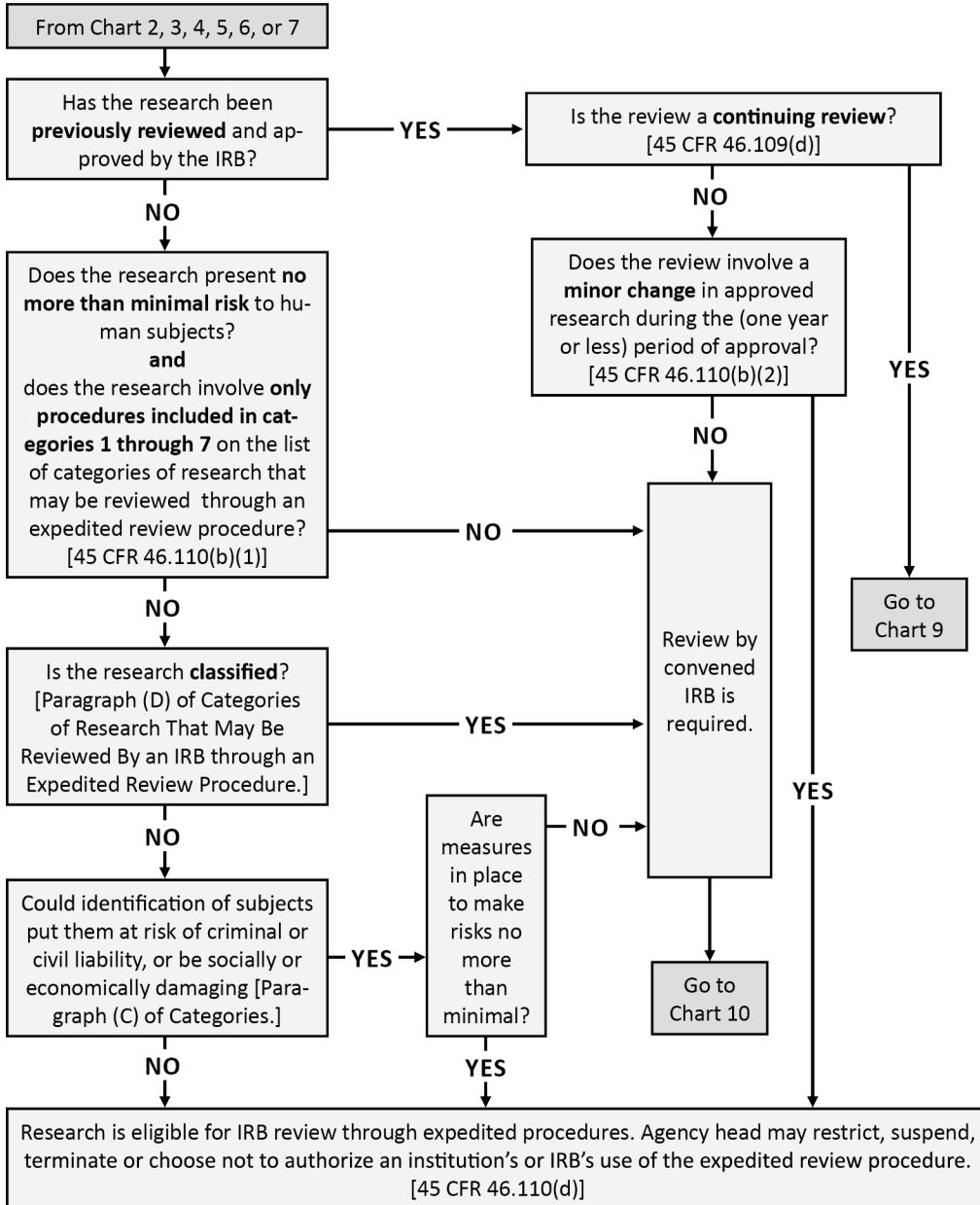
September 24, 2004



**CHART 8:**

**May the IRB Review Be Done by Expedited Procedures Under 45 CFR 46.110?\***

September 24, 2004

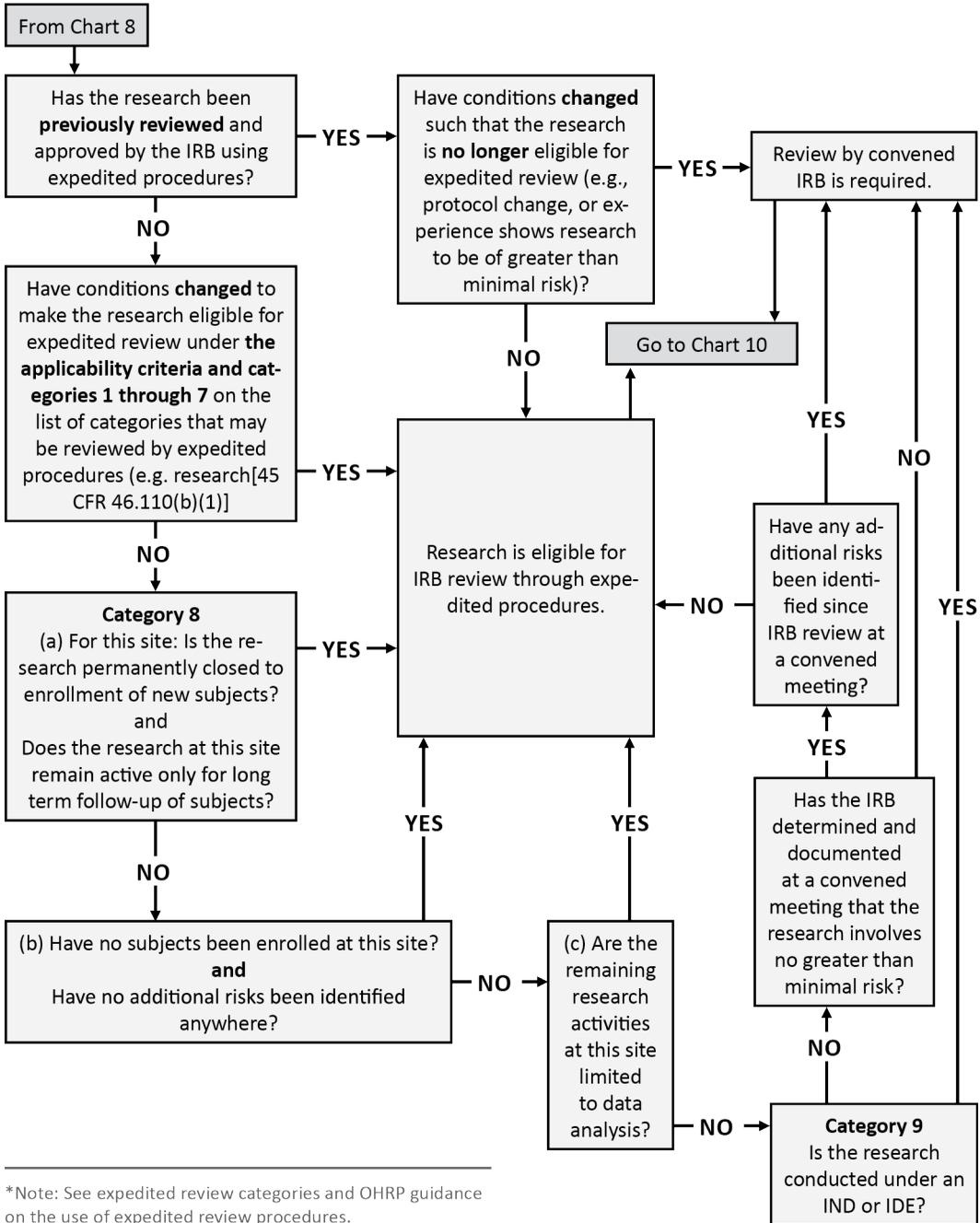


\*Note: See expedited review categories and OHRP guidance on the use of expedited review procedures.

**CHART 9:**

**Can Continuing Review be Done by Expedited Procedures Under 45 CFR 46.110?**

September 24, 2004

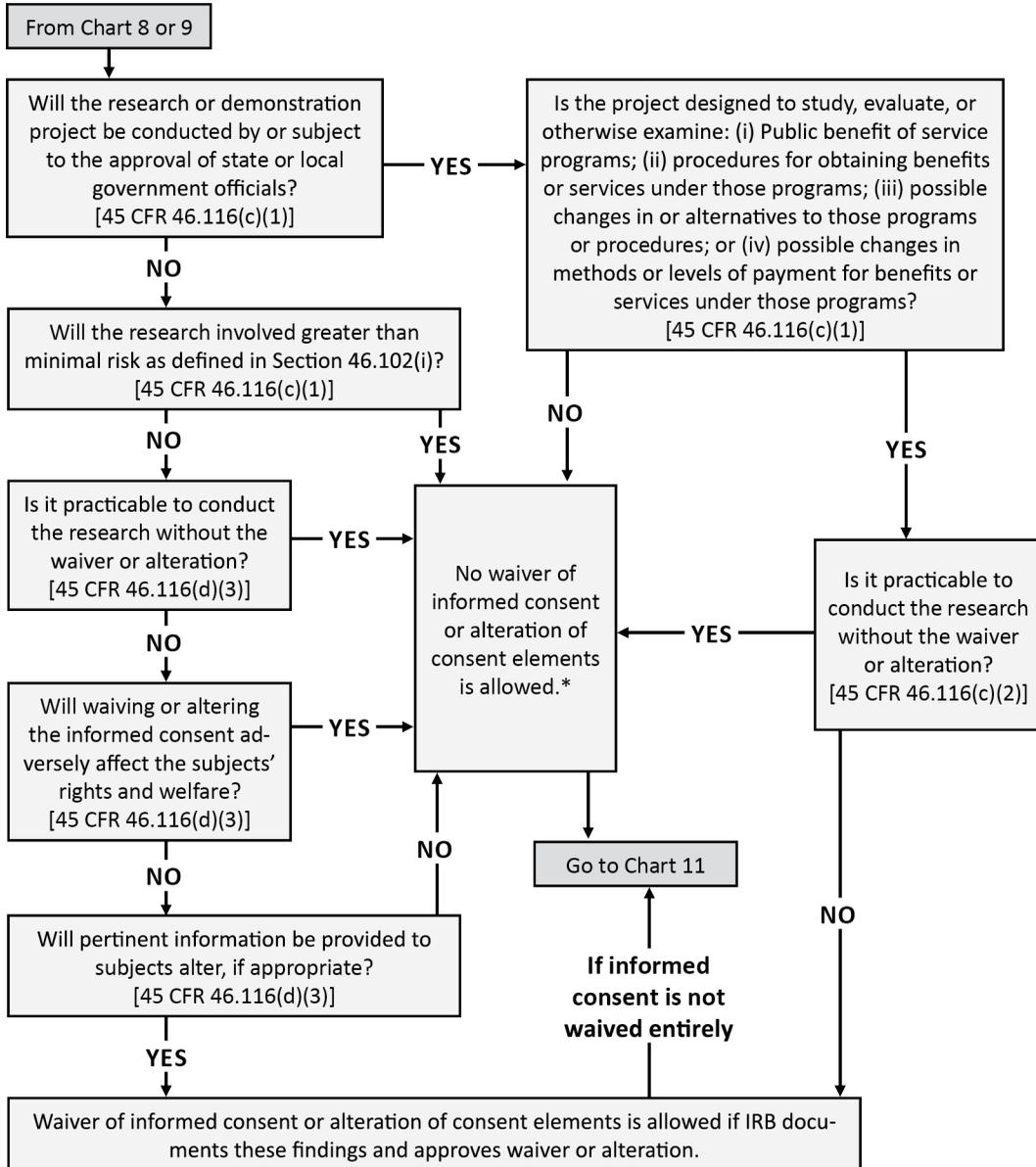


\*Note: See expedited review categories and OHRP guidance on the use of expedited review procedures.

**CHART 10:**

**Can Informed Consent Be Waived or Consent Elements Be Altered Under 45 CFR 46.116(c) or (d)?\*\***

September 24, 2004

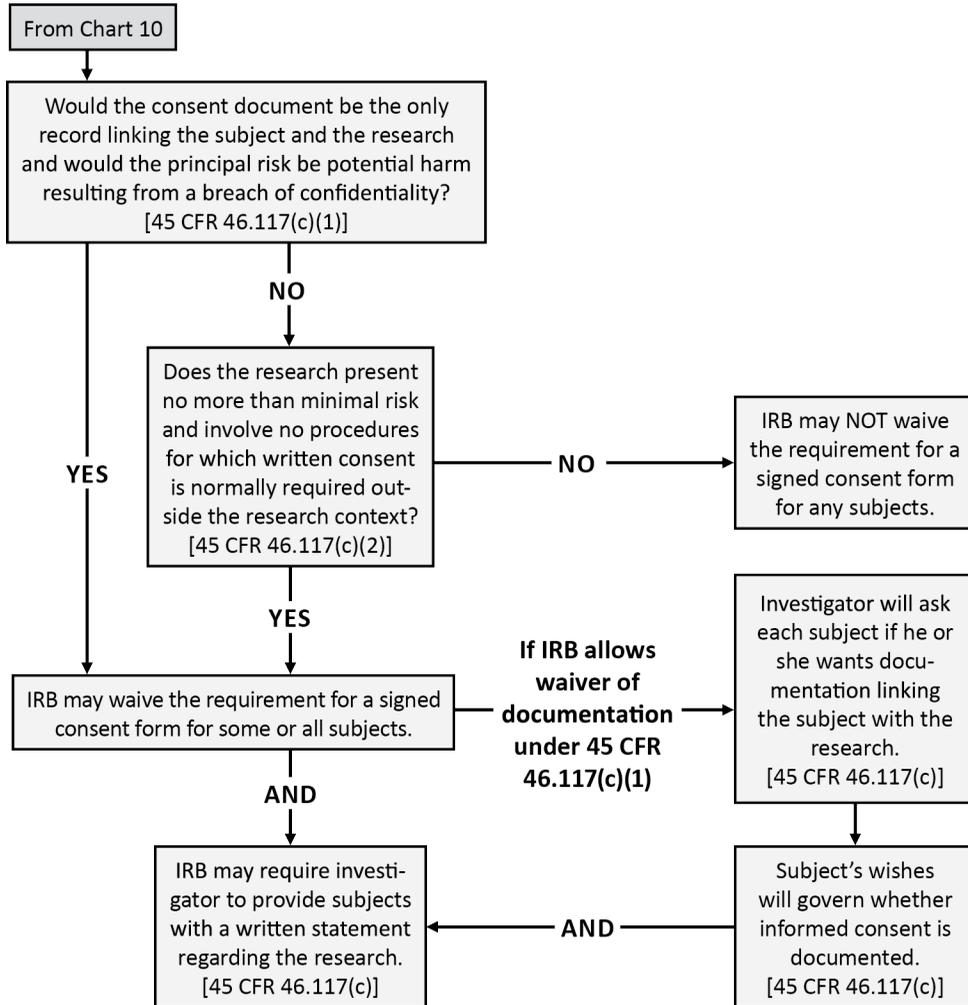


\*Note: See OHRP guidance on informed consent requirements in emergency research.

**CHART 11:**

**Can Documentation of Informed Consent Be Waived Under 45 CFR 46.117(c)?**

September 24, 2004



CODE OF FEDERAL REGULATIONS  
 TITLE 45  
 PUBLIC WELFARE DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 NATIONAL INSTITUTES OF HEALTH  
 OFFICE FOR PROTECTION FROM RESEARCH RISKS  
 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**

- Section 46.101 To what does this policy apply?
- 46.102 Definitions.
- 46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.
- 46.104 [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.

### **SUBPART B—Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research**

- Section 46.201 To what do these regulations apply?  
46.202 Definitions.  
46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.  
46.204 Research involving pregnant women or fetuses.  
46.205 Research involving neonates.  
46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.  
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.

### **SUBPART C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects**

- Section 46.301 Applicability.  
46.302 Purpose.  
46.303 Definitions.  
46.304 Composition of Institutional Review Boards where prisoners are involved.  
46.305 Additional duties of the Institutional Review Boards where prisoners are involved.  
46.306 Permitted research involving prisoners.

### **SUBPART D—Additional Protections for Children Involved as Subjects in Research**

- Section 46.401 To what do these regulations apply?  
46.402 Definitions.  
46.403 IRB duties.  
46.404 Research not involving greater than minimal risk.  
46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.  
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.  
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.  
46.408 Requirements for permission by parents or guardians and for assent by children.  
46.409 Wards.

Authority: 5 U.S.C. 301; 42 U.S.C. 289(a).

**SUBPART E—Registration of Institutional Review Boards**

- Section 46.501 What IRBs must be registered?  
46.502 What information must be provided when registering an IRB?  
46.503 When must an IRB be registered?  
46.504 How must an IRB be registered?  
46.505 When must IRB registration information be renewed or updated?

*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.*



TITLE 45  
CODE OF FEDERAL REGULATIONS  
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**

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.

[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.

(j) Certifications means the official notification by the institution to the supporting department or agency, 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.

**§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 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.

(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 record keeping 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.

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[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.

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[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.

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[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.

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[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.

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[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 Secretary, 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 federal wide 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 federal wide 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. Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure.

## 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.

## 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, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml 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 non disfiguring 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 gum base 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 prophylactic 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 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 non research 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.

[Source: 63 FR 60364-60367, November 9, 1998.]



**Office for Human Research Protections (OHRP)**  
**Department of Health and Human Services (HHS)**

# Guidance on the Engagement of Institutions in Human Subjects Research

NOTE: This guidance document replaces two previous OHRP guidance documents: (1) “Engagement of Institutions in Research” (January 26, 1999); and (2) “Engagement of Pharmaceutical Companies in HHS-Supported Research (PDF)” (December 23, 1999).

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:** October 16, 2008

**Scope:** This guidance document applies to research involving human subjects that is conducted or supported by the Department of Health and Human Services (HHS). When an institution is engaged in non-exempt human subjects research that is conducted or supported by HHS, it must satisfy HHS regulatory requirements related to holding an assurance of compliance and certifying institutional review board (IRB) review and approval. This guidance document describes:

1. Scenarios that, in general, would result in an institution being considered engaged in a human subjects research project;
2. Scenarios that would result in an institution being considered not engaged in a human subjects research project; and

3. IRB review considerations for cooperative research in which multiple institutions are engaged in the same non-exempt human subjects research project.

The scenarios below of situations where an institution is generally considered to be engaged or not engaged in human subjects research conducted or supported by HHS apply to all types of institutions, including academic or other non-profit organizations, institutions operating commercial repositories, and pharmaceutical or medical device companies.

**Target Audience:** IRBs, research administrators and other relevant institutional officials, investigators, and funding agencies that may be responsible for review or oversight of human subjects research conducted or supported by HHS.

## I. Background

Before engaging in HHS-conducted or -supported human subjects research that is not exempt under HHS regulations at 45 CFR 46.101(b), an institution must:

1. Hold or obtain an OHRP-approved Federalwide Assurance (FWA) [45 CFR 46.103(a)]; and,
2. Certify to the HHS agency conducting or supporting the research that the research has been reviewed and approved by an IRB designated in the FWA and will be subject to continuing review by an IRB [45 CFR 46.103(b)].

Note that the IRBs designated under an FWA may include IRBs of other institutions or independent IRBs. For more information on FWAs and how to designate an IRB of another institution on an FWA, see the following:

- OHRP Assurances Webpage (<http://www.hhs.gov/ohrp/assurances/index.html>)
- OHRP FWA Frequently Asked Questions (<http://answers.hhs.gov/ohrp/categories/1565>),
- OHRP Guidance on Extension of an FWA to Cover Collaborating Individual Investigators and Introduction of the Individual Investigator Agreement (<http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.html>), and
- OHRP IRB Registration Frequently Asked Questions (<http://answers.hhs.gov/ohrp/categories/1565>).

The following definitions are relevant for determining whether an institution's activities are covered by the HHS protection of human subjects regulations (45 CFR part 46), and whether the institution is engaged in human subjects research.

**Research** is defined in 45 CFR 46.102(d) as follows:

**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.

**Human subject** is defined in 45 CFR 46.102(f) as follows:

**Human subject** means a living individual about whom an investigator (whether professional or student) conducting research obtains

1. (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.

**Institution** is defined in 45 CFR 46.102(b) as any public or private entity or agency (including federal, state, and other agencies).

For purposes of this document, an institution's employees or agents refers to individuals who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. "Employees and agents" can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

## II. When to Use This Guidance

This guidance should only be applied to activities that have been determined to be research involving human subjects that are not exempt under HHS regulations at 45 CFR 46.101(b). The following guidance documents available on the OHRP website may be helpful in determining whether research involves human subjects and also whether it is exempt: OHRP Human Subject Regulations Decision Charts (see OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (PDF) (see <http://www.hhs.gov/ohrp/policy/cdebiol.pdf>).

Once an activity is determined to involve non-exempt human subjects research, this guidance should be used to determine whether an institution involved in some aspect of the research is engaged in that human subjects research, because if it is, certain regulatory requirements apply. Specifically, institutions that are engaged in non-exempt human subjects research are required by 45 CFR part 46 to:

1. Hold or obtain an applicable OHRP-approved FWA [45 CFR 46.103(a)]; and
2. Certify to the HHS agency conducting or supporting the research that the research has been reviewed and approved by an IRB designated in the FWA, and will be subject to continuing review by an IRB [45 CFR 46.103(b)].

OHRP recognizes that many institutions and individuals (e.g., the principal investigator, statistical centers, community physicians, educators, data repositories) may work together on various aspects of a human subjects research project. However, not all participating institutions and individuals need to be covered by an FWA or certify IRB review and approval of the research to the HHS agency conducting or supporting the research. This guidance aims to assist institutions in determining whether they must meet those requirements, that is, whether they are engaged in activities covered by the regulations.

### **III. Interpretation of Engagement of Institutions in Human Subjects Research**

In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. The following two sections apply these concepts.

The scenarios in Section A describe the types of institutional involvement that generally would result in an institution being engaged in human subjects research. The scenarios in Section B include the types of institutional involvement that would result in an institution being not engaged in human subjects research, but these scenarios are not intended to be all-inclusive. There may be additional scenarios in which an institution would be not engaged in human subjects research. The determination of engagement depends on the specific facts of a research study and may be complex.

In applying this guidance, it is important to note that at least one institution must be determined to be engaged in any non-exempt human subjects research project that is conducted or supported by HHS (45 CFR 46.101(a)).

In the scenarios below, employees and agents are individuals acting on behalf of the institution, exercising institutional authority or responsibility, or performing institutionally designated activities.

## A. Institutions Engaged in Human Subjects Research

In general, institutions are considered engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would need to hold or obtain OHRP-approved FWAs and certify IRB review and approval to HHS) when the involvement of their employees or agents in that project includes any of the following:

1. Institutions that receive an award through a grant, contract, or cooperative agreement directly from HHS for the non-exempt human subjects research (i.e. awardee institutions), even where all activities involving human subjects are carried out by employees or agents of another institution.
2. Institutions whose employees or agents intervene for research purposes with any human subjects of the research by performing invasive or noninvasive procedures.

Examples of invasive or noninvasive procedures include drawing blood; collecting buccal mucosa cells using a cotton swab; administering individual or group counseling or psychotherapy; administering drugs or other treatments; surgically implanting medical devices; utilizing physical sensors; and utilizing other measurement procedures.

[See scenarios B.(1), B.(2), and B.(3) below for limited exceptions.]

3. Institutions whose employees or agents intervene for research purposes with any human subject of the research by manipulating the environment.

Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions.

[See scenarios B.(1) and B.(3) below for limited exceptions.]

4. Institutions whose employees or agents interact for research purposes with any human subject of the research.

Examples of interacting include engaging in protocol dictated communication or interpersonal contact; asking someone to provide a specimen by voiding or spitting into a specimen container; and conducting research interviews or administering questionnaires.

[See scenarios B.(1), B.(2), B.(3), and B.(4) below for limited exceptions.]

5. Institutions whose employees or agents obtain the informed consent of human subjects for the research.
6. Institutions whose employees or agents obtain for research purposes identifiable private information or identifiable biological specimens from any source for the research. It is important to note that, in general, institutions whose employees or agents obtain identifiable private information or identifiable specimens for non-exempt human subjects research are considered

engaged in the research, even if the institution's employees or agents do not directly interact or intervene with human subjects. In general, obtaining identifiable private information or identifiable specimens includes, but is not limited to:

- a. Observing or recording private behavior;
- b. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens provided by another institution; and
- c. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens already in the possession of the investigators.

In general, OHRP considers private information or specimens to be individually identifiable as defined in 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

[See scenarios B.(1), B.(2), B.(3), B.(7), B.(8), B.(9), and B.(10) below for limited exceptions.]

## **B. Institutions Not Engaged in Human Subjects Research**

Institutions would be considered not engaged in an HHS-conducted or -supported non-exempt human subjects research project (and, therefore, would not need to hold an OHRP-approved FWA or certify IRB review and approval to HHS) if the involvement of their employees or agents in that project is limited to one or more of the following. The following are scenarios describing the types of institutional involvement that would make an institution not engaged in human subjects research; there may be additional such scenarios:

1. Institutions whose employees or agents perform commercial or other services for investigators provided that all of the following conditions also are met:
  - a. The services performed do not merit professional recognition or publication privileges;
  - b. The services performed are typically performed by those institutions for non-research purposes; and
  - c. The institution's employees or agents do not administer any study intervention being tested or evaluated under the protocol.

The following are some examples, assuming the services described would not merit professional recognition or publication privileges:

- An appropriately qualified laboratory whose employees perform routine serum chemistry analyses of blood samples for investigators as a commercial service.
- A transcription company whose employees transcribes research study interviews as a commercial service.

- A hospital whose employees obtain blood through a blood draw or collect urine and provide such specimens to investigators as a service.
  - A radiology clinic whose employees perform chest x-rays and send the results to investigators as a service.
2. Institutions (including private practices) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that all of the following conditions also are met:
- a. The institution's employees or agents do not administer the study interventions being tested or evaluated under the protocol;
  - b. The clinical trial-related medical services are typically provided by the institution for clinical purposes;
  - c. The institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and
  - d. When appropriate, investigators from an institution engaged in the research retain responsibility for:
    - i. Overseeing protocol-related activities; and
    - ii. Ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.

Note that institutions (including private practices) not initially selected as research sites whose employees or agents administer the interventions being tested or evaluated in the study—such as administering either of two chemotherapy regimens as part of an oncology clinical trial evaluating the safety and effectiveness of the two regimens—generally would be engaged in human subjects research (see scenario B.(3) below for a limited exception). If such an institution does not have an FWA, its employees or agents may be covered by the FWA of another institution that is engaged in the research through an Individual Investigator Agreement. See <http://www.hhs.gov/ohrp/policy/guidanceonalternativetofwa.pdf>.

3. Institutions (including private practices) not initially selected as a research site whose employees or agents administer the study interventions being tested or evaluated under the protocol limited to a one-time or short-term basis (e.g., an oncologist at the institution administers chemotherapy to a research subject as part of a clinical trial because the subject unexpectedly goes out of town, or is unexpectedly hospitalized), provided that all of the following conditions also are met:
  - a. An investigator from an institution engaged in the research determines that it would be in the subject's best interest to receive the study interventions being tested or evaluated under the protocol;
  - b. The institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research;
  - c. Investigators from the institution engaged in the research retain responsibility for:
    - i. Overseeing protocol-related activities;
    - ii. Ensuring the study interventions are administered in accordance with the IRB-approved protocol; and
    - iii. Ensuring appropriate arrangements are made for reporting protocol-related data to investigators at the engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol; and
  - d. An IRB designated on the engaged institution's FWA is informed that study interventions being tested or evaluated under the protocol have been administered at an institution not selected as a research site.
4. Institutions whose employees or agents:
  - a. Inform prospective subjects about the availability of the research;
  - b. Provide prospective subjects with information about the research (which may include a copy of the relevant informed consent document and other IRB approved materials) but do not obtain subjects' consent for the research or act as representatives of the investigators;
  - c. Provide prospective subjects with information about contacting investigators for information or enrollment; and/or
  - d. Seek or obtain the prospective subjects' permission for investigators to contact them.

An example of this would be a clinician who provides patients with literature about a research study at another institution, including a copy of the informed consent document, and obtains permission from the patient to provide the patient's name and telephone number to investigators.

5. Institutions (e.g., schools, nursing homes, businesses) that permit use of their facilities for intervention or interaction with subjects by investigators from another institution.

Examples would be a school that permits investigators from another institution to conduct or distribute a research survey in the classroom; or a business that permits investigators from another institution to recruit research subjects or to draw a blood sample at the work site for research purposes.

6. Institutions whose employees or agents release to investigators at another institution identifiable private information or identifiable biological specimens pertaining to the subjects of the research.

Note that in some cases the institution releasing identifiable private information or identifiable biological specimens may have institutional requirements that would need to be satisfied before the information or specimens may be released, and/or may need to comply with other applicable regulations or laws. In addition, if the identifiable private information or identifiable biological specimens to be released were collected for another research study covered by 45 CFR part 46, then the institution releasing such information or specimens should:

- a. Ensure that the release would not violate the informed consent provided by the subjects to whom the information or biological specimens pertain (under 45 CFR 46.116), or
- b. If informed consent was waived by the IRB, ensure that the release would be consistent with the IRB's determinations that permitted a waiver of informed consent under 45 CFR 46.116 (c) or (d).

Examples of institutions that might release identifiable private information or identifiable biological specimens to investigators at another institution include:

- a. Schools that release identifiable student test scores;
- b. An HHS agency that releases identifiable records about its beneficiaries; and
- c. Medical centers that release identifiable human biological specimens.

Note that, in general, the institutions whose employees or agents obtain the identifiable private information or identifiable biological specimens from the releasing institution would be engaged in human subjects research. [See scenario A.(6) above.]

7. Institutions whose employees or agents:
  - a. Obtain coded private information or human biological specimens from another institution involved in the research that retains a link to individually identifying information (such as name or social security number); and

- b. Are unable to readily ascertain the identity of the subjects to whom the coded information or specimens pertain because, for example:
- The institution's employees or agents and the holder of the key enter into an agreement prohibiting the release of the key to the those employees or agents under any circumstances;
  - The releasing institution has IRB-approved written policies and operating procedures applicable to the research project that prohibit the release of the key to the institution's employees or agents under any circumstances; or
  - There are other legal requirements prohibiting the release of the key to the institution's employees or agents.

For purposes of this document, coded means that:

- d. Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, and/or combination thereof (i.e., the code); and
- e. A key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Although this scenario resembles some of the language in OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens, it is important to note that OHRP's Guidance on Research Involving Coded Private Information or Biological Specimens addresses when research involving coded private information or specimens is or is not research involving human subjects, as defined in 45 CFR 46.102(f) (see <http://www.dhhs.gov/ohrp/policy/cdebiol.pdf>). As stated above in Section II., this Guidance on Engagement of Institutions in Human Subjects Research should only be applied to research projects that have been determined to involve human subjects and that are not exempt under HHS regulations at 45 CFR 46.101(b).

8. Institutions whose employees or agents access or utilize individually identifiable private information only while visiting an institution that is engaged in the research, provided their research activities are overseen by the IRB of the institution that is engaged in the research.
9. Institutions whose employees or agents access or review identifiable private information for purposes of study auditing (e.g. a government agency or private company will have access to individually identifiable study data for auditing purposes).
10. Institutions whose employees or agents receive identifiable private information for purposes of satisfying U.S. Food and Drug Administration reporting requirements.
11. Institutions whose employees or agents author a paper, journal article, or presentation describing a human subjects research study.

#### IV. IRB Review Considerations for Cooperative Research

OHRP notes that multiple institutions may be engaged in the same non-exempt human subjects research project. For such cooperative research projects, institutions may enter into joint review arrangements, rely upon the review of another qualified IRB, or make similar arrangements to avoid duplication of effort, in accordance with HHS regulations at 45 CFR 46.114.

When an institution is engaged in only part of a cooperative research project along the lines of scenarios A.(2), A.(3), A.(4), A.(5), or A.(6), the institution must ensure that the IRB(s) designated under its FWA reviews and approves the part(s) of the research in which the institution is engaged. For example, an institution operating the statistical center for a multicenter trial that receives identifiable private information from multiple other institutions must ensure that an IRB designated under its FWA reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center. In such a case, the IRB should ensure that the statistical center has sufficient mechanisms in place to adequately protect the privacy of subjects and maintain the confidentiality of the data. When an institution is engaged in only part of a cooperative research project, the reviewing IRB may decide to review the entire research study, even if information about the entire study is not necessary to approve the institution's part of the research under 45 CFR 46.111.

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](mailto:ohrp@hhs.gov).

[<http://www.hhs.gov/ohrp/policy/engage08.html>]



CODE OF FEDERAL REGULATIONS  
TITLE 21  
FOOD AND DRUGS  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PART 50  
PROTECTION OF HUMAN SUBJECTS

## II. Informed Consent

### SUBPART A—General Provisions

- Section 50.1 Scope.  
50.3 Definitions.

### SUBPART B—Informed Consent of Human Subjects

- Section 50.2 General requirements for informed consent.  
50.23 Exception from general requirements.  
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### SUBPART C—[Reserved]

### SUBPART D—Additional Safeguards for Children in Clinical Investigations

- Section 50.50 IRB duties.  
50.51 Clinical investigations not involving greater than minimal risk.  
50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.  
50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.  
50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.  
50.55 Requirements for permission by parents or guardians and for assent by children.  
50.56 Wards.

## 21 CFR PART 50—PROTECTION OF HUMAN SUBJECTS

[Source: 45 FR 36390, May 30, 1980, unless otherwise noted.]



**NOTE:** The Food and Drug Administration is issuing final regulations addressing the safety reporting requirements for investigational new drug applications (INDs) found in 21 CFR part 312 and for bioavailability and bioequivalence studies found in 21 CFR part 320.

This final rule is expected to improve the quality of safety reports submitted to FDA, thereby enhancing the safety of patients in clinical trials. The final rule lays out clear, internationally harmonized definitions and standards so that critical safety information about investigational new drugs will be accurately and rapidly reported to the agency, minimizing uninformative reports and enhancing reporting of meaningful, interpretable information.

## **PART 50—PROTECTION OF HUMAN SUBJECTS**

### Subpart B—Informed Consent of Human Subjects

#### **§50.25—Elements of informed consent.**

(a) Basic elements of informed consent. 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 and that notes the possibility that the Food and Drug Administration may inspect the records.
- (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, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that 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.

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

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

(d) Nothing in these 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.

## Subpart A—General Provisions

### §50.1—Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Additional specific obligations and commitments of, and standards of conduct for, persons who sponsor or monitor clinical investigations involving particular test articles may also be found in other parts (e.g., parts 312 and 812). Compliance with these parts is intended to protect the rights and safety of subjects involved in investigations filed with the Food and Drug Administration pursuant to sections 403, 406, 409, 412, 413, 502, 503, 505, 510, 513-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 36390, May 30, 1980; 46 FR 8979, Jan. 27, 1981, as amended at 63 FR 26697, May 13, 1998; 64 FR 399, Jan. 5, 1999; 66 FR 20597, Apr. 24, 2001]

### §50.3—Definitions.

As used in this part:

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040et seq. as amended (21 U.S.C. 321-392)).

(b) Application for research or marketing permit includes:

(1) A color additive petition, described in part 71.

(2) A food additive petition, described in parts 171 and 571.

(3) Data and information about a substance submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in 170.30 and 570.30.

(4) Data and information about a food additive submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in 180.1.

(5) Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) An investigational new drug application, described in part 312 of this chapter.

(7) A new drug application, described in part 314.

(8) Data and information about the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) Data and information about an over-the-counter drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) Data and information about a prescription drug for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An application for a biologics license, described in part 601 of this chapter.

(13) Data and information about a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) Data and information about an in vitro diagnostic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

- (15) An Application for an Investigational Device Exemption, described in part 812.
- (16) Data and information about a medical device submitted as part of the procedures for classifying these devices, described in section 513.
- (17) Data and information about a medical device submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.
- (18) An application for premarket approval of a medical device, described in section 515.
- (19) A product development protocol for a medical device, described in section 515.
- (20) Data and information about an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.
- (21) Data and information about an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in 1010.4.
- (22) Data and information about an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in 1010.5.
- (23) Data and information about a clinical study of an infant formula when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.
- (24) Data and information submitted in a petition for a nutrient content claim, described in 101.69 of this chapter, or for a health claim, described in 101.70 of this chapter.
- (25) Data and information from investigations involving children submitted in a new dietary ingredient notification, described in 190.6 of this chapter.
- (c) Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is 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 provisions of part 58 of this chapter, regarding nonclinical laboratory studies.
- (d) Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(e) Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(f) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

(g) Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(h) Institution means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

(i) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

(j) Test article means any drug (including a 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 act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

(k) 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.

(l) 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.

(m) Family member means any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

(n) Assent means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent.

(o) Children means 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.

(p) Parent means a child's biological or adoptive parent.

(q) Ward means a child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law.

(r) Permission means the agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation.

(s) Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

[45 FR 36390, May 30, 1980, as amended at 46 FR 8950, Jan. 27, 1981; 54 FR 9038, Mar. 3, 1989; 56 FR 28028, June 18, 1991; 61 FR 51528, Oct. 2, 1996; 62 FR 39440, July 23, 1997; 64 FR 399, Jan. 5, 1999; 64 FR 56448, Oct. 20, 1999; 66 FR 20597, Apr. 24, 2001; 78 FR 12950, Feb. 26, 2013]



## Subpart B—Informed Consent of Human Subjects

### §50.20—General requirements for informed consent.

Except as provided in 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations 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.

[46 FR 8951, Jan. 27, 1981, as amended at 64 FR 10942, Mar. 8, 1999]

### §50.23—Exception from general requirements.

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

- (1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained from the subject 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) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(c) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(d)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved the Secretary of Defense must first request such a determination from the President, and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by 56.115(a)(2) of this chapter.

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate followup to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations.

(e)(1) Obtaining informed consent for investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents will be deemed feasible unless, before use of the test article, both the investigator (e.g., clinical laboratory director or other responsible individual) and a physician who is not otherwise participating in the clinical investigation make the determinations and later certify in writing all of the following:

(i) The human subject is confronted by a life-threatening situation necessitating the use of the investigational in vitro diagnostic device to identify a chemical, biological, radiological, or nuclear agent that would suggest a terrorism event or other public health emergency.

(ii) Informed consent cannot be obtained from the subject because:

(A) There was no reasonable way for the person directing that the specimen be collected to know, at the time the specimen was collected, that there would be a need to use the investigational in vitro diagnostic device on that subject's specimen; and

(B) Time is not sufficient to obtain consent from the subject without risking the life of the subject.

(iii) Time is not sufficient to obtain consent from the subject's legally authorized representative.

(iv) There is no cleared or approved available alternative method of diagnosis, to identify the chemical, biological, radiological, or nuclear agent that provides an equal or greater likelihood of saving the life of the subject.

(2) If use of the investigational device is, in the opinion of the investigator (e.g., clinical laboratory director or other responsible person), required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (e)(1) of this section in advance of using the investigational device, the determinations of the investigator shall be made and, within 5 working days after the use of the device, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(3) The investigator must submit the documentation required in paragraph (e)(1) or (e)(2) of this section to the IRB within 5 working days after the use of the device.

(4) An investigator must disclose the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in the report to the subject's health care provider and in any report to public health authorities. The investigator must provide the IRB with the information required in 50.25 (except for the information described in 50.25(a)(8)) and the procedures that will be used to provide this information to each subject or the subject's legally authorized representative at the time the test results are provided to the subject's health care provider and public health authorities.

(5) The IRB is responsible for ensuring the adequacy of the information required in section 50.25 (except for the information described in 50.25(a)(8)) and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.

(6) No State or political subdivision of a State may establish or continue in effect any law, rule, regulation or other requirement that informed consent be obtained before an investigational in vitro diagnostic device may be used to identify chemical, biological, radiological, or nuclear agent in suspected terrorism events and other potential public health emergencies that is different from, or in addition to, the requirements of this regulation.

[46 FR 8951, Jan. 27, 1981, as amended at 55 FR 52817, Dec. 21, 1990; 64 FR 399, Jan. 5, 1999; 64 FR 54188, Oct. 5, 1999; 71 FR 32833, June 7, 2006]

#### **§50.24—Exception from informed consent requirements for emergency research.**

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

[61 FR 51528, Oct. 2, 1996]

**§50.25—Elements of informed consent.**

(a) Basic elements of informed consent. 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 and that notes the possibility that the Food and Drug Administration may inspect the records.

(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, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that 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.

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

(c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

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

(e) Nothing in these 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.

[46 FR 8951, Jan. 27, 1981, as amended at 76 FR 270, Jan. 4, 2011]

**§50.27—Documentation of informed consent.**

(a) Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy shall be given to the person signing the form.

(b) Except as provided in 56.109(c), the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by 50.25. 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.

(2) A short form written consent document stating that the elements of informed consent required by 50.25 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 the 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.

[46 FR 8951, Jan. 27, 1981, as amended at 61 FR 57280, Nov. 5, 1996]



## Subpart C—[Reserved]

## Subpart D—Additional Safeguards for Children in Clinical Investigations

### §50.50—IRB duties.

In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51, 50.52, or 50.53 and the conditions of all other applicable sections of this subpart D.

### §50.51—Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds that: (a) No greater than minimal risk to children is presented; (b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in 50.55.

[78 FR 12951, Feb. 26, 2013]

### § 50.52—Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which 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, may involve children as subjects only if the IRB finds and documents 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 50.55.

**§50.53—Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects’ disorder or condition.**

Any clinical investigation within the scope described in 50.1 and 56.101 of this chapter in which 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 that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds and documents 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 that is of vital importance for the understanding or amelioration of the subjects’ disorder or condition; and
- (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

**§50.54—Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.**

If an IRB does not believe that a clinical investigation within the scope described in 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:

- (a) The IRB finds and documents that the clinical investigation 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 Commissioner of Food and Drugs, 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, determines either:
  - (1) That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or

(2) That the following conditions are met:

- (i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- (ii) The clinical investigation will be conducted in accordance with sound ethical principles; and
- (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 50.55.

**§50.55—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 D, the IRB must 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.

(b) In determining whether children are capable of providing assent, the IRB must 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 clinical investigations under a particular protocol, or for each child, as the IRB deems appropriate.

(c) The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) That the intervention or procedure involved in the clinical investigation 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 clinical investigation.

(d) Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement if it finds and documents that:

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

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

(3) The clinical investigation could not practicably be carried out without the waiver; and

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

(e) In addition to the determinations required under other applicable sections of this subpart D, the IRB must determine, in accordance with and to the extent that consent is required under part 50, that the permission of each child's parents or guardian is granted.

(1) Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient, if consistent with State law, for clinical investigations to be conducted under 50.51 or 50.52.

(2) Where clinical investigations are covered by 50.53 or 50.54 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 if consistent with State law.

(f) Permission by parents or guardians must be documented in accordance with and to the extent required by 50.27.

(g) When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

#### **§ 50.56—Wards.**

(a) Children who are wards of the State or any other agency, institution, or entity can be included in clinical investigations approved under 50.53 or 50.54 only if such clinical investigations are:

(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 clinical investigation is approved under paragraph (a) of this section, the IRB must require appointment of an advocate for each child who is a ward.

(1) The advocate will serve in addition to any other individual acting on behalf of the child as guardian or in loco parentis.

(2) One individual may serve as advocate for more than one child.

(3) The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the clinical investigation.

(4) The advocate must not be associated in any way (except in the role as advocate or member of the IRB) with the clinical investigation, the investigator(s), or the guardian organization.

Authority: 21 U.S.C 321, 343, 346, 346a, 348, 350a, 350b, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 379e, 381; 42 U.S.C. 216, 241, 262, 263b-263n.

Source: 45 FR 36390, May 30, 1980, unless otherwise noted.



Office for Protection from Research Risks\*

## TIPS ON INFORMED CONSENT

Source: <http://www.hhs.gov/ohrp/policy/ictips.html>

The process of obtaining informed consent must comply with the requirements of 45 CFR 46.116. The documentation of informed consent must comply with 45 CFR 46.117. The following comments may help in the development of an approach and proposed language by investigators for obtaining consent and its approval by IRBs:

- Informed consent is a process, not just a form. Information must be presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is a fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand. Therefore, informed consent language and its documentation (especially explanation of the study's purpose, duration, experimental procedures, alternatives, risks, and benefits) must be written in "lay language", (i.e. understandable to the people being asked to participate). The written presentation of information is used to document the basis for consent and for the subjects' future reference. The consent document should be revised when deficiencies are noted or when additional information will improve the consent process.
- Use of the first person (e.g., "I understand that ...") can be interpreted as suggestive, may be relied upon as a substitute for sufficient factual information, and can constitute coercive influence over a subject. Use of scientific jargon and legalese is not appropriate. Think of the document primarily as a teaching tool not as a legal instrument.
- Describe the overall experience that will be encountered. Explain the research activity, how it is experimental (e.g., a new drug, extra tests, separate research records, or nonstandard means of management, such as flipping a coin for random assignment or other design issues). Inform the human subjects of the reasonably foreseeable harms, discomforts, inconvenience and risks that are associated with the research activity. If additional risks are identified during the course of the research, the consent process and documentation will require revisions to inform subjects as they are recontacted or newly contacted.

- Describe the benefits that subjects may reasonably expect to encounter. There may be none other than a sense of helping the public at large. If payment is given to defray the incurred expense for participation, it must not be coercive in amount or method of distribution.
- Describe any alternatives to participating in the research project. For example, in drug studies the medication(s) may be available through their family doctor or clinic without the need to volunteer for the research activity.
- The regulations insist that the subjects be told the extent to which their personally identifiable private information will be held in confidence. For example, some studies require disclosure of information to other parties. Some studies inherently are in need of a Certificate of Confidentiality which protects the investigator from involuntary release (e.g., subpoena) of the names or other identifying characteristics of research subjects. The IRB will determine the level of adequate requirements for confidentiality in light of its mandate to ensure minimization of risk and determination that the residual risks warrant involvement of subjects.
- If research-related injury (i.e. physical, psychological, social, financial, or otherwise) is possible in research that is more than minimal risk (see 45 CFR 46.102[g]), an explanation must be given of whatever voluntary compensation and treatment will be provided. Note that the regulations do not limit injury to “physical injury”. This is a common misinterpretation.
- The regulations prohibit waiving or appearing to waive any legal rights of subjects. Therefore, for example, consent language must be carefully selected that deals with what the institution is voluntarily willing to do under circumstances, such as providing for compensation beyond the provision of immediate or therapeutic intervention in response to a research-related injury. In short, subjects should not be given the impression that they have agreed to and are without recourse to seek satisfaction beyond the institution’s voluntarily chosen limits.
- The regulations provide for the identification of contact persons who would be knowledgeable to answer questions of subjects about the research, rights as a research subject, and research-related injuries. These three areas must be explicitly stated and addressed in the consent process and documentation. Furthermore, a single person is not likely to be appropriate to answer questions in all areas. This is because of potential conflicts of interest or the appearance of such. Questions about the research are frequently best answered by the investigator(s). However, questions about the rights of research subjects or research-related injuries (where applicable) may best be referred to those not on the research team. These questions could be addressed to the IRB, an ombudsman, an ethics committee, or other informed administrative body. Therefore, each consent document can be expected to have at least two names with local telephone numbers for contacts to answer questions in these specified areas.

- The statement regarding voluntary participation and the right to withdraw at any time can be taken almost verbatim from the regulations (45 CFR 46.116[a][8]). It is important not to overlook the need to point out that no penalty or loss of benefits will occur as a result of both not participating or withdrawing at any time. It is equally important to alert potential subjects to any foreseeable consequences to them should they unilaterally withdraw while dependent on some intervention to maintain normal function.
- Don't forget to ensure provision for appropriate additional requirements which concern consent. Some of these requirements can be found in §§46.116(b), 46.205(a)(2), 46.207(b), 46.208(b), 46.209(d), 46.305(a)(5-6), 46.408(c), and 46.409(b).The IRB may impose additional requirements that are not specifically listed in the regulations to ensure that adequate information is presented in accordance with institutional policy and local law.

Revised 3/16/93



## III. Subject Recruitment

# Guidance for Institutional Review Boards & Clinical Investigators from FDA Information Sheets

### Recruiting Study Subjects

FDA requires that an Institutional Review Board (IRB) review and have authority to approve, require modifications in, or disapprove all research activities covered by the IRB regulations [21 CFR 56.109(a)]. An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects [21 CFR 56.107(a) and 56.111]. In fulfilling these responsibilities, an IRB is expected to review all the research documents and activities that bear directly on the rights and welfare of the subjects of proposed research. The protocol, the consent document and, for studies conducted under the Investigational New Drug (IND) regulations, the investigator's brochure are examples of documents that the IRB should review. The IRB should also review the methods and material that investigators propose to use to recruit subjects.

#### A. Media Advertising

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study, is not in and of itself, an objectionable practice. Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects. Not included are:

(1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects)

(2) news stories, and

(3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review. However, when the clinical investigator decides at a later date to advertise for subjects, the advertising may be considered an amendment to the ongoing study. When such advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means, as provided by 21 CFR 56.110(b)(2). When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

FDA expects IRBs to review the advertising to assure that it is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence.

[21 CFR 50.20, 50.25, 56.111(a)(3), 56.111(b) and 812.20(b)(11).]

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

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

Advertising for recruitment into investigational drug, biologic or device studies should not use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational. A phrase such as "receive new treatments" leads study subjects to believe they will be receiving newly improved products of proven worth.

Advertisements should not promise "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type.

Generally, FDA believes that any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items.

1. the name and address of the clinical investigator and/or research facility;
2. the condition under study and/or the purpose of the research;
3. in summary form, the criteria that will be used to determine eligibility for the study;
4. a brief list of participation benefits, if any (e.g., a no-cost health examination);
5. the time or other commitment required of the subjects; and
6. the location of the research and the person or office to contact for further information.

## **B. Receptionist Scripts**

The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects. In some cases personal and sensitive information is gathered about the individual. The IRB should have assurance that the information will be appropriately handled. A simple statement such as "confidentiality will be maintained" does not adequately inform the IRB of the procedures that will be used.

Examples of issues that are appropriate for IRB review: What happens to personal information if the caller ends the interview or simply hangs up? Are the data gathered by a marketing company? If so, are names, etc. sold to others? Are names of non-eligibles maintained in case they would

qualify for another study? Are paper copies of records shredded or are readable copies put out as trash? The acceptability of the procedures would depend on the sensitivity of the data gathered, including personal, medical and financial.

Also see FDA Information Sheets: “A Guide to Informed Consent Documents” and “Payment to Research Subjects.”

### **Payment to Research Subjects**

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. It is not uncommon for subjects to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or non-existent. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Also see FDA Information Sheets: “A Guide to Informed Consent Documents” and “Recruiting Study Subjects.”

### **Screening Tests Prior to Study Enrollment**

For some studies, the use of screening tests to assess whether prospective subjects are appropriate candidates for inclusion in studies is an appropriate pre-entry activity. While an investigator may discuss availability of studies and the possibility of entry into a study with a prospective

subject without first obtaining consent, informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out).When wash-out is done in anticipation of or in preparation for the research, it is part of the research.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

Clinical screening procedures for research eligibility are considered part of the subject selection and recruitment process and, therefore, require IRB oversight. If the screening qualifies as a minimal risk procedure [21 CFR 56.102(i)], the IRB may choose to use expedited review procedures [21 CFR 56.110].The IRB should receive a written outline of the screening procedure to be followed and how consent for screening will be obtained. The IRB may find it appropriate to limit the scope of the screening consent to a description of the screening tests and to the reasons for performing the tests including a brief summary description of the study in which they may be asked to participate. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document [21 CFR 56.109(c)]. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would then be followed.

Certain clinical tests, such as for HIV infection, may have State requirements regarding (1) the information that must be provided to the participant, (2) which organizations have access to the test results and (3) whether a positive result has to be reported to the health department. Prospective subjects should be informed of any such requirements and how an unfavorable test result could affect employment or insurance before the test is conducted. The IRB may wish to confirm that such tests are required by the protocol of the study.

Also see FDA Information Sheet: “Recruiting Study Subjects.”



## IV. Research on Human Specimens: Are You Conducting Human Subjects Research?

Your research may fall under the umbrella of human subjects even if you aren't working on humans directly. For example, some basic research on samples would be considered human subjects, while research taking a different approach is not. This is a complicated topic with many rules and regulations, so tread carefully and read on to learn more.

To determine if NIH will consider your study to involve human subjects, read the information below. You can find more detailed information in the SF 424 Application Guide or the PHS 398.

### Determine if Your Study Involves Human Subjects

HHS' Protection of Human Subjects in 45 CFR Part 46 defines a human subject as a living person about whom an investigator obtains either 1) data through intervening or interacting with the person or 2) identifiable, private information.

Before you decide whether your research involves human subjects, make sure you understand NIH's Guidance on Research Involving Coded Private Information or Biological Specimens. Go to the glossary links in the right column for definitions of these key terms:

- Human subjects.
- Individually identifiable.
- Private information.
- Research using human specimens or data.

In general if you're using coded private information, data, or specimens, NIH will consider your research to involve human subjects unless it meets both of the following conditions:

- You are not collecting samples by interacting or intervening with living people.
- None of the investigators or collaborators listed in the application can identify the subjects through coded private information or specimens (e.g., an investigator's access to identity is prohibited by a written agreement).

If any investigator involved in the research can determine a subject's identity or has access to identifiers, the research is considered to involve human subjects and human subjects requirements apply. Read more details in Office for Human Research Protections (OHRP)'s Guidance on Research Involving Coded Private Information or Biological Specimens.

Also see the HHS Human Subjects Regulations Decision Charts and NIH's flow chart for Research Involving Private Information or Biological Specimens.

If you still have questions about whether your application has human subjects, ask your IRB or IEC before writing your application. NIH recommends that investigators not be given the authority to determine whether research involves human subjects.

When applying for human subjects research, check "yes" for human subjects on the application face page. For more help, go to the following on NIAID's Web site:

- Decision Trees for Human Subjects Requirements
- Private Information or Biological Specimens in Human Subjects Research and Human Subjects in the Human Subjects Resources questions and answers

Most requirements for protecting human subjects are codified in the law, 45 CFR Part 46.

**Multiproject applications.** If you are submitting a multiproject application, you are applying for human subjects research even if only one component includes human subjects. Complete human subjects requirements for each component of the application. Go to our Guidance for Preparing a Multiproject Research Application.

### **Additional Resources**

- Human Subjects (General) checklist
- Office of Extramural Research's FAQs from Applicants Human Subjects Research and FAQs About Research Using Human Specimens, Cell Lines or Data
- HHS Office for Human Research Protections
  - Human Research questions and answers
  - International Compilation of Human Subjects Research Protections—to use, click on document title, scroll down, and click on a country.
- Planning a Human Subjects Application checklist
- Phase III Clinical Trials checklist
- Trans NIAID Clinical Research Toolkit

### **Is Your Research Exempt?**

When we refer to human subjects research in this document, we are referring to nonexempt research. The six human subjects exemptions rarely apply to NIAID.

Almost all research at NIAID is either human subjects or not human subjects. To determine whether you are conducting human subjects research, see the section Determine if Your Study Involves Human Subjects.

To determine whether your research is exempt, go to OHRP's Is an Activity Research Involving Human Subjects? If think your research may be exempt, contact your program officer.

### **When Your Research Is Exempt**

#### **If your program officer agrees that an exemption applies, do the following:**

- Justify the exemption in the Protection of Human Subjects section of the Research Plan, as follows:
  - For electronic applications, include a justification in the PHS 398 Research Plan component of the Grant Application Package.
  - For paper applications, create a section called Protection of Human Subjects in the narrative part of your application and include your justification there.
- Resolve any concerns for human subjects protections to NIH's satisfaction, keeping in mind:
  - While you must justify the exemption, you don't need documentation from your IRB or IEC that your research is exempt.
  - While it is rare that NIAID will return your application if you claim an exemption and it is incorrect or improperly justified, reviewers will assess your justification and it may affect your score.
  - If your research is exempt but you still have access to basic characteristics about your subject population, you should include that information. If basic characteristics are unknown for exemption 4, indicate that in your plan.
  - For all exemptions, if you know the criteria for including or excluding any subpopulation, you must identify that in your Research Plan.

#### **For exemptions other than exemption 4:**

- Provide certification of human subjects education for key personnel or send just-in-time (at the time of award). Read the Human Subjects Certifications: Training SOP.
- Submit completed Targeted/Planned Enrollment Tables and Inclusion Enrollment Report Tables when appropriate.

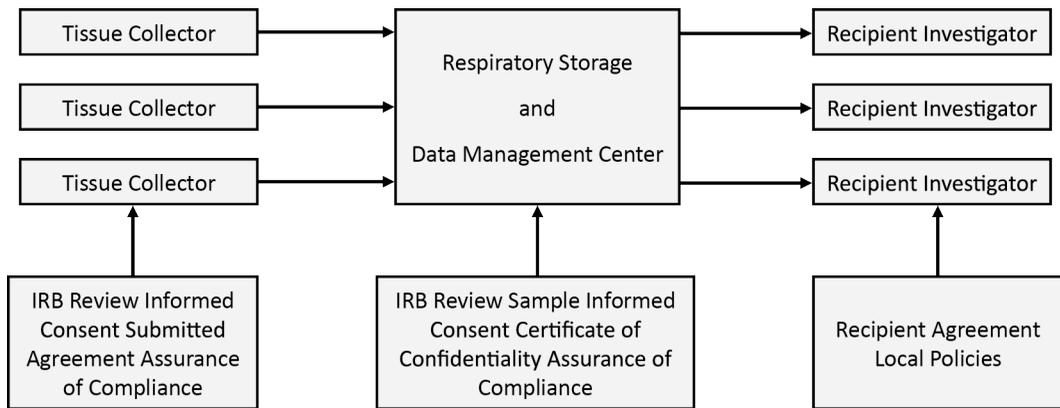
#### **Additional Resources**

- Code of Federal Regulations: Protection of Human Subjects OHRP Web site
- Human Subjects questions and answers
- OHRP Human Subjects Assurance Training
- Private Information or Biological Specimens in Human Subjects Research questions and answers



**OFFICE FOR PROTECTION FROM RESEARCH RISKS\***  
**Issues to Consider in the Research Use of Stored Data or Tissues**  
**November 7, 1997**

**Human Tissue Repositories** collect, store, and distribute human tissue materials for research purposes. Repository activities involve three components: (i) the **collectors** of tissue samples; (ii) the **repository** storage and data management center; and (iii) the **recipient** investigators.



If supported by the Department of Health and Human Services (HHS), each component must satisfy certain **regulatory requirements**.

Operation of the Repository and its data management center should be subject to **oversight by an Institutional Review Board (IRB)**. The IRB should review and approve a protocol specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB should also review and approve a sample collection protocol and informed consent document for distribution to tissue collectors and their local IRBs. A **Certificate of Confidentiality** should be obtained to protect confidentiality of repository specimens and data.

For Additional Information: Office for Human Research Protections Department of Health and Human Services 6100 Executive Boulevard, Suite 3B01, MSC-7507 Rockville, MD 20892-7507 301-402-5189 / FAX 301-402-2071 / E-MAIL OHRP@hhs.gov<sup>5</sup>

<sup>5</sup>\*Now Office for Human Research Protections (OHRP).



Office for Human Research Protections (OHRP)  
Department of Health and Human Services (HHS)

## Guidance on the Genetic Information Nondiscrimination Act: Implications for Investigators and Institutional Review Boards

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:** March 24, 2009

**Scope:** This document applies to non-exempt human subjects research conducted or supported by HHS. It provides background information regarding the Genetic Information Nondiscrimination Act of 2008 (GINA) and discusses some of the implications of GINA for investigators who conduct, and institutional review boards (IRBs) that review, non-exempt human subjects research involving genetic testing or the collection of genetic information (hereinafter referred to as “genetic research”), particularly with respect to the criteria for IRB approval of research and the requirements for obtaining informed consent.

The information presented in the background section of this document is intended for general information purposes only. While the background section does not cover all of the specifics of GINA, it does provide an explanation of the statute to assist those involved in the conduct or oversight of research to understand the law and its prohibitions related to discrimination based on genetic information in (a) coverage provided either by health insurers or by employment-based group health plans (hereinafter referred to as “health coverage”), and (b) employment. This information should not be considered legal advice. In addition, some of the provisions of GINA discussed involve issues for which the rules have not been finalized, and this information is subject to revision based on publication of regulations.

**Target Audience:** Investigators who conduct, and IRBs that review, genetic research involving human subjects that is conducted or supported by HHS.

### **Background on GINA:**

GINA is a Federal law that prohibits discrimination in health coverage and employment based on genetic information. GINA, together with already existing nondiscrimination provisions of the Health Insurance Portability and Accountability Act, generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or an individual's family members, or using such information for decisions regarding coverage, rates, or preexisting conditions. GINA also prohibits employers from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment. The parts of the law relating to health coverage (Title I) generally will take effect between May 22, 2009, and May 21, 2010, and those relating to employment (Title II) will take effect on November 21, 2009<sup>1</sup>. GINA requires regulations pertaining to both titles to be completed by May 2009. Once GINA takes effect, it generally will prohibit discrimination based on genetic information in connection with health coverage and employment, no matter when the information was collected.

GINA provides a baseline level of protection against genetic discrimination for all Americans. Many states already have laws that protect against genetic discrimination in health insurance and employment situations. However, the degree of protection they provide varies widely, and while most provisions are less protective than GINA, some are more protective. All entities that are subject to GINA must, at a minimum, comply with all applicable GINA requirements, and may also need to comply with more protective State laws.

GINA defines genetic information as information about:

- An individual's genetic tests (including genetic tests done as part of a research study);
- Genetic tests of an individual's family members (defined as dependents and up to and including the degree relatives);
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology;
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.

GINA defines a genetic test as an analysis of human DNA, RNA, chromosomes, proteins, or metabolites that detect genotypes, mutations, or chromosomal changes. Routine tests that do not detect genotypes, mutations, or chromosomal changes, such as complete blood counts, cholesterol tests, and liver enzyme tests, are not considered genetic tests under GINA. Also, under GINA, genetic tests do not include analyses of proteins or metabolites that are directly related to

a manifested disease, disorder, or pathological condition that could reasonably be detected by a health care professional with appropriate training and expertise in the field of medicine involved.

GINA includes a “research exception” to the general prohibition against health insurers or group health plans requesting that an individual undergo a genetic test. This exception allows health insurers and group health plans engaged in research to request (but not require) that an individual undergo a genetic test. This exception permits the request to be made but imposes the following requirements:

- The request must be made pursuant to research that complies with HHS regulations at 45
- CFR part 46, or equivalent Federal regulations, and any applicable state or local laws for the protection of human subjects in research;
- There must be clear indication that participation is voluntary and that non-compliance has no effect on enrollment or premiums or contribution amounts;
- No genetic information collected or acquired as part of the research may be used for underwriting purposes;
- The health insurer or group health plan must notify the Federal government in writing that it is conducting activities pursuant to this research exception and provide a description of the activities conducted; and
- The health insurer or group health plan must comply with any future conditions that the

Federal government may require for activities conducted under this research exception. GINA’s provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance. For example, GINA does not make it illegal for a life insurance company to discriminate based on genetic information. In addition, GINA’s provisions prohibiting discrimination by employers based on genetic information generally do not apply to employers with fewer than 15 employees. For health coverage provided by a health insurer to individuals, GINA does not prohibit the health insurer from determining eligibility or premium rates for an individual based on the manifestation of a disease or disorder in that individual. For employment-based health coverage provided by group health plans, GINA permits the overall premium rate for an employer to be increased because of the manifestation of a disease or disorder of an individual enrolled in the plan, but the manifested disease or disorder of one individual cannot be used as genetic information about other group members to further increase the premium. GINA also does not prohibit health insurers or health plan administrators from obtaining and using genetic test results in making payment determinations.

For additional details regarding the provisions of GINA see

<http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf>.

<sup>4</sup>The effective date of the insurance provisions is not the same in all cases because for group health plans, Title I will take effect at the start of the group health plan’s first year beginning after May 21, 2009. Because some health plans do not designate their “plan years” to correspond to a calendar year, there will be variation among plans as to when Title I takes effect for the plans. However, for individual health insurers, GINA will take effect May 22, 2009. Genetic information does not include information about the sex or age of any individual.

**Guidance:**

Given that GINA has implications regarding the actual or perceived risks of genetic research and an individual's willingness to participate in such research, investigators and IRBs should be aware of the protections provided by GINA as well as the limitations in the law's scope and effect. IRBs should consider the provisions of GINA when assessing whether genetic research satisfies the criteria required for IRB approval of research, particularly whether the risks are minimized and reasonable in relation to anticipated benefits and whether there are adequate provisions in place to protect the privacy of subjects and maintain the confidentiality of their data. GINA is also relevant to informed consent. When investigators develop, and IRBs review, consent processes and documents for genetic research, they should consider whether and how the protections provided by GINA should be reflected in the consent document's description of risks and provisions for assuring the confidentiality of the data.

**A. GINA and the Criteria for IRB Approval of Research**

When reviewing proposed or ongoing genetic research, IRBs should consider the protections provided by GINA when determining whether the research satisfies the following criteria required for IRB approval of research:

- 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 which are 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 subjects, and the importance of the knowledge that may reasonably be expected to result (45 CFR
- 46.111(a)(2)); and
- When appropriate, there are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data (45 CFR 46.111(a)(7)).

Among the risks typically associated with genetic research, investigators, IRBs, and research subject advocates, among others, have identified the potential adverse impact on insurability or employability if genetic information about the subject obtained as part of the research was disclosed to, or sought by, insurers or employers. When the provisions of GINA take effect, the risk of such harms will be decreased with respect to health coverage and most employment.

Since a decrease in risk should favorably affect the risk-benefit assessment for genetic research, the protections provided by GINA have direct relevance for IRBs that are assessing whether genetic research satisfies the criteria under 45 CFR 46.111(a)(1), (2), and (7).

Even though the provisions of GINA related to health coverage generally will take effect between May 22, 2009, and May 21, 2010, and those related to employment will take effect on November 21, 2009, investigators and IRBs should be aware that the protections provided by GINA are pertinent to genetic research that is conducted prior to these effective dates because these protections eventually will extend to genetic information obtained as part of any research

study regardless of when the research was conducted. Therefore, IRBs conducting initial or continuing review of genetic research prior to GINA's stipulated effective dates should take into account the protections to be provided by GINA when assessing whether such research satisfies the criteria required for IRB approval of research referenced above.

When making the above determinations required under 45 CFR 46.111(a), IRBs also need to be cognizant that (1) GINA's provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance; and (2) GINA's provisions prohibiting discrimination by employers based on genetic information generally do not apply to employers with fewer than 15 employees.

## **B. GINA and the Requirements for Informed Consent**

When investigators develop, and IRBs review, consent processes and documents for genetic research, they should consider the protections provided by GINA, particularly with respect to the following elements of informed consent that must be provided to subjects (unless an IRB has approved an alteration or waiver of these requirements in accordance with the requirements of HHS regulations at 45 CFR 46.116(c) or (d)):

- A description of any reasonably foreseeable risks or discomforts to the subjects (45 CFR 46.116(a)(2)); and
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (45 CFR 46.116(a)(5)).

Investigators and IRBs must ensure that descriptions of the reasonably foreseeable risks of genetic research and any statements describing the extent to which confidentiality of records identifying the subject will be maintained do not overstate the protections provided by GINA (45 CFR 46.116(a)). Key points for investigators and IRBs to consider when describing these protections include the following:

- The provisions of GINA related to health coverage generally will take effect between May 22, 2009, and May 21, 2010, and those related to employment will take effect on November 21, 2009.
- The discrimination protections provided by GINA address health coverage and employment only.
- GINA's provisions prohibiting discrimination in health coverage based on genetic information do not extend to life insurance, disability insurance, or long-term care insurance. Therefore, to the extent that the risks of genetic research include potential adverse impact on a subject's ability to obtain life insurance, disability insurance, or long-term care insurance if genetic information about the subject obtained as part of the research was disclosed to or sought by such insurers, GINA has no effect on these risks.
- GINA generally does not apply to employers with fewer than 15 employees. Therefore, subjects who are or will be employed by such employers receive none of the GINA protections that prohibit discrimination in employment on the basis of genetic information.

Even though, as explained above, the provisions of GINA related to health coverage do not take effect until some time within a year of May 21, 2009, and those related to employment do not take effect until November 21, 2009, investigators and IRBs need to be aware that GINA has implications for how risks are described for genetic research conducted prior to these effective dates.

Regardless of when genetic information was obtained or collected, GINA restricts the use of such information as soon as GINA becomes effective for a particular plan or insurance policy. For example, even if an individual participated in a research study involving genetic testing in 6 January 2009, a health insurer or health plan administrator, once GINA's protections related to health coverage take effect, will be prohibited from (1) requesting information about the results of the genetic tests performed in that research study or about the individual's participation in that research study (unless the health insurer or health plan administrator has satisfied the requirements of the research exception discussed in the background section above), and (2) using such information for decisions regarding coverage, rates, or preexisting conditions for that individual if such information is disclosed in some way to the insurer or health plan administrator.

Likewise, effective November 21, 2009, GINA generally will prohibit employers with 15 or more employees from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment, regardless of when the information was obtained or collected. For example, even if an individual participated in a research study involving genetic counseling in January 2009, an employer with 15 or more employees, as of November 21, 2009, will be prohibited from using genetic information resulting from that individual's participation in that research for hiring, firing, or promotion decisions or for any decisions regarding terms of employment for that individual.

OHRP recommends that for genetic research undergoing initial or continuing review investigators and IRBs consider whether consent processes and documents should include language regarding the protections provided by GINA, and if so, ensure that such language accurately describes the impact of GINA on the risks and confidentiality protections for such research. The following is one example of sample language regarding the protections provided under GINA that investigators and IRBs could consider including in informed consent documents for such research, if it is determined that including such language is appropriate:

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

IRBs should feel free to revise the sample language above as appropriate based on the nature of the research and the types of human subjects involved.

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](mailto:ohrp@hhs.gov).



TITLE 21 – FOOD AND DRUGS  
FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PART 312 – INVESTIGATIONAL NEW DRUG

## V. Investigational New Drug Application

### Subpart A—General Provisions

#### §312.1—Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

#### §312.2—Applicability.

(a) Applicability. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201et seq.)).

(b) Exemptions.

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

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

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

- (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
  - (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
  - (v) The investigation is conducted in compliance with the requirements of 312.7.
- (2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a ) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b ) it is shipped in compliance with 312.160.
- (ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a ) blood grouping serum; (b ) reagent red blood cells; and (c ) anti-human globulin.
- (3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 312.160.
- (4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.
- (5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.
- (6) A clinical investigation involving an exception from informed consent under 50.24 of this chapter is not exempt from the requirements of this part.
- (c) Bioavailability studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of 320.31.
- (d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.
- (e) Guidance. FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

**§312.3—Definitions and interpretations.**

(a) The definitions and interpretations of terms contained in section 201 of the Act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (secs. 201–902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301–392)).

Clinical investigation means 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.

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

FDA means the Food and Drug Administration.

IND means an investigational new drug application. For purposes of this part, “IND” is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.”

Independent ethics committee (IEC) means a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection. An institutional review board (IRB), as defined in §56.102(g) of this chapter and subject to the requirements of part 56 of this chapter, is one type of IEC.

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical investigation ( i.e. , under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Subinvestigator” includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act or a biologics license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

[52 FR 8831, Mar. 19, 1987, as amended at 64 FR 401, Jan. 5, 1999; 64 FR 56449, Oct. 20, 1999; 73 FR 22815, Apr. 28, 2008]

### **§312.6—Labeling of an investigational new drug.**

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use.”

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

(c) The appropriate FDA Center Director, according to the procedures set forth in §§201.26 or 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

[52 FR 8831, Mar. 19, 1987, as amended at 72 FR 73599, Dec. 28, 2007]

### **§312.7—Promotion of investigational drugs.**

(a) Promotion of an investigational new drug. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) Commercial distribution of an investigational new drug. A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) Prolonging an investigation. A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19476, May 22, 1987; 67 FR 9585, Mar. 4, 2002; 74 FR 40899, Aug. 13, 2009]

### **§312.8—Charging for investigational drugs under an IND.**

(a) General criteria for charging.

(1) A sponsor must meet the applicable requirements in paragraph (b) of this section for charging in a clinical trial or paragraph (c) of this section for charging for expanded access to an investigational drug for treatment use under subpart I of this part, except that sponsors need not fulfill the requirements in this section to charge for an approved drug obtained from another entity not affiliated with the sponsor for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, for use of the approved drug as an active control).

(2) A sponsor must justify the amount to be charged in accordance with paragraph (d) of this section.

(3) A sponsor must obtain prior written authorization from FDA to charge for an investigational drug.

(4) FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

(b) Charging in a clinical trial

(1) Charging for a sponsor's drug. A sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must:

(i) Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

(ii) Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

(iii) Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to

manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

(2) Duration of charging in a clinical trial. Unless FDA specifies a shorter period, charging may continue for the length of the clinical trial.

(c) Charging for expanded access to investigational drug for treatment use.

(1) A sponsor who wishes to charge for expanded access to an investigational drug for treatment use under subpart I of this part must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

(2) For expanded access under §312.320 (treatment IND or treatment protocol), such assurance must include:

(i) Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned;

(ii) Evidence of adequate progress in the development of the drug for marketing approval; and

(iii) Information submitted under the general investigational plan (§312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(3) The authorization to charge is limited to the number of patients authorized to receive the drug under the treatment use, if there is a limitation.

(4) Unless FDA specifies a shorter period, charging for expanded access to an investigational drug for treatment use under subpart I of this part may continue for 1 year from the time of FDA authorization. A sponsor may request that FDA reauthorize charging for additional periods.

(d) Costs recoverable when charging for an investigational drug.

(1) A sponsor may recover only the direct costs of making its investigational drug available.

(i) Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

(ii) Indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale)

and research and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

(2) For expanded access to an investigational drug for treatment use under §§312.315 (intermediate-size patient populations) and 312.320 (treatment IND or treatment protocol), in addition to the direct costs described in paragraph (d)(1)(i) of this section, a sponsor may recover the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

(3) To support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the calculation is consistent with the requirements of paragraphs (d)(1) and, if applicable, (d)(2) of this section. The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

[74 FR 40899, Aug. 13, 2009]

### **§312.10—Waivers.**

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

- (1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;
- (2) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or
- (3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds that the sponsor's noncompliance would not pose a significant and unreasonable risk to human subjects of the investigation and that one of the following is met:

- (1) The sponsor's compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved;
- (2) The sponsor's proposed alternative satisfies the requirement; or
- (3) The applicant's submission otherwise justifies a waiver.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9585, Mar. 4, 2002]



## Subpart B—Investigational New Drug Application (IND)

### §312.20—Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to § 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to § 312.2(a) until the investigation is subject to an IND which is in effect in accordance with § 312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 62 FR 32479, June 16, 1997]

### §312.21—Phases of an investigation.

An IND may be submitted for one or more phases of an investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general the they may overlap. These three phases of an investigation are a follows:

(a) Phase 1.

(1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.

(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(b) Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) Phase 3. Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

### **§312.22—General principles of the IND submission.**

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in § 312.23 should be followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed phases are conducted sequentially, for a commercially

sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

### §312.23—IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) Cover sheet (Form FDA-1571). A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under § 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred— may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) A table of contents.

(3) Introductory statement and general investigational plan.

(i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

(A)The rationale for the drug or the research study;

(B)The indication(s) to be studied;

(C)The general approach to be followed in evaluating the drug;

(D)The kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate);

(E) The estimated number of patients to be given the drug in those studies; and

(F) Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) Investigator's brochure. If required under § 312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) Protocols.

(i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with § 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation— an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(A) A statement of the objectives and purpose of the study.

(B) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(C) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(D) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(E) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(F) A description of the observations and measurements to be made to fulfill the objectives of the study.

(G) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) Chemistry, manufacturing, and control information.

(i) As appropriate for the particular investigations covered by the IND, a section describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(A) Drug substance. A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy relevant requirements in this paragraph.

(B) Drug product. A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy certain requirements in this paragraph.

(C) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(D) Labeling. A copy of all labels and labeling to be provided to each investigator.

(E) Environmental analysis requirements. A claim for categorical exclusion under §25.30 or 25.31 or an environmental assessment under §25.40.

(8) Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the

results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) Toxicology.

(A) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(B) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) Previous human experience with the investigational drug. A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

(10) Additional information. In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) Radioactive drugs. If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) Pediatric studies. Plans for assessing pediatric safety and effectiveness.

(iv) Other information. A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

(11) Relevant information. If requested by FDA, any other relevant information needed for review of the application.

(b) **Information previously submitted.** The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(c) **Material in a foreign language.** The sponsor shall submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) **Number of copies.** The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e) **Numbering of IND submissions.** Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

**(f) Identification of exception from informed consent.** If the investigation involves an exception from informed consent under § 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in § 50.24 of this chapter.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51529, Oct. 2, 1996; 62 FR 40599, July 29, 1997; 63 FR 66669, Dec. 2, 1998; 65 FR 56479, Sept. 19, 2000]

### **§312.30—Protocol amendments.**

Once an IND is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made. Whenever a sponsor intends to conduct a clinical investigation with an exception from informed consent for emergency research as set forth in § 50.24 of this chapter, the sponsor shall submit a separate IND for such investigation.

(a) New protocol. Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met:

(1) The sponsor has submitted the protocol to FDA for its review; and

(2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

(b) Changes in a protocol.

(1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

(i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

(ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

(iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(A) The sponsor has submitted the change to FDA for its review; and

(B) The change has been approved by the IRB with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(ii) Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with § 56.104(c).

(c) New investigator. A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under § 312.315 or 312.320.. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

(d) Content and format. A protocol amendment is required to be prominently identified as such (i.e., “Protocol Amendment: New Protocol”, “Protocol Amendment: Change in Protocol”, or “Protocol Amendment: New Investigator”), and to contain the following:

(1)(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator’s name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator’s study as is required under § 312.23(a)(6)(iii)(b).

(2) Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(3) If the sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.

(e) When submitted. A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 61 FR 51530, Oct. 2, 1996; 67 FR 9585, Mar. 4, 2002; 74 FR 40942, Aug. 13, 2009]

### **§312.31—Information amendments.**

(a) Requirement for information amendment. A sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:

- (1) New toxicology, chemistry, or other technical information; or
- (2) A report regarding the discontinuance of a clinical investigation.

(b) Content and format of an information amendment. An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

- (1) A statement of the nature and purpose of the amendment.
- (2) An organized submission of the data in a format appropriate for scientific review.
- (3) If the sponsor desires FDA to comment on an information amendment, a request for such comment.

(c) When submitted. Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 53 FR 1918, Jan. 25, 1988; 67 FR 9585, Mar. 4, 2002]

**§312.32—IND safety reports.**

(a) Definitions. The following definitions of terms apply to this section:

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

*Life-threatening adverse event or life-threatening suspected adverse reaction* . 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.

*Serious adverse event or serious suspected adverse reaction* . 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.

*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. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

*Unexpected adverse event or unexpected suspected adverse reaction* . 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.

(b) Review of safety information . The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any sources, foreign or domestic, including information derived from any clinical or from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

(c) (1) IND safety reports.

The sponsor must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of this section. In each IND safety report, the sponsor must identify 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.

(i) Serious and unexpected suspected adverse reaction . The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

(A) 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)

(B) 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);

(C) 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.

(ii) *Findings from other studies* . The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would 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.

(iii) *Findings from animal or in vitro testing* . The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would 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.

(iv) *Increased rate of occurrence of serious suspected adverse reactions* . 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.

(v) *Submission of IND safety reports* . The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a FDA Form 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

(c) (2) *Unexpected fatal or life-threatening suspected adverse reaction reports* . The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

(c) (3) *Reporting format or frequency* . FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

(c) (4) *Investigations of marketed drugs* . A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the postmarketing safety reporting requirements (e.g., 310.305, 314.80, and 600.80 of this chapter).

(c) (5) *Reporting study endpoints*. Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under paragraph (c) of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under 312.32(c)(1)(i) as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

(d) Followup.

(1) The sponsor shall promptly investigate all safety information received by it.

(2) Relevant followup information to an IND safety report shall be submitted as soon as the relevant information is available and must be identified as such, i.e., "Followup IND Safety Report."

(3) If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is so reportable, the sponsor shall report such suspected adverse reaction in an IND safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

(e) Disclaimer. A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 62 FR 52250, Oct. 7, 1997; 67 FR 9585, Mar. 4, 2002; 75 FR 59961, Sept. 29, 2010]

### **312.33—Annual reports.**

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief report of the progress of the investigation that includes:

(a) Individual study information. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) Summary information. Information obtained during the previous year's clinical and nonclinical investigations, including

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings

(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan or the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under § 312.23(a)(3)(iv).

(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting

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[75 CFR 59961, Sept. 29, 2010]

### **§312.38—Withdrawal of an IND.**

(a) At any time a sponsor may withdraw an elective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investors notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with § 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

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[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

## Subpart C—Administrative Actions

### §312.40—General requirements for use of an investigational new drug in a clinical investigation.

(a) An investigational new drug may be used in a clinical investigation if the following conditions are met:

- (1) The sponsor of the investigation submits an IND for the drug to FDA; the IND is in effect under paragraph (b) of this section; and the sponsor complies with all applicable requirements in this part and parts 50 and 56 with respect to the conduct of the clinical investigations; and
- (2) Each participating investigator conducts his or her investigation in compliance with the requirements of this part and parts 50 and 56.

(b) An IND goes into effect:

- (1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under §312.42; or
- (2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND.

(c) A sponsor may ship an investigational new drug to investigators named in the IND:

- (1) Thirty days after FDA receives the IND; or
- (2) On earlier FDA authorization to ship the drug.

(e) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

### **§312.41—Comment and advice on an IND.**

(a) FDA may at any time during the course of the investigation communicate with the sponsor orally or in writing about deficiencies in the IND or about FDA's need for more data or information.

(b) On the sponsor's request, FDA will provide advice on specific matters relating to an IND. Examples of such advice may include advice on the adequacy of technical data to support an investigational plan, on the design of a clinical trial, and on whether proposed investigations are likely to produce the data and information that is needed to meet requirements for a marketing application.

(c) Unless the communication is accompanied by a clinical hold order under §312.42, FDA communications with a sponsor under this section are solely advisory and do not require any modification in the planned or ongoing clinical investigations or response to the agency.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

### **§312.42—Clinical holds and requests for modification.**

(a) General. A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

(b) Grounds for imposition of clinical hold —

(1) Clinical hold of a Phase 1 study under an IND. FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that:

(i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;

(ii) The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND;

(iii) The investigator brochure is misleading, erroneous, or materially incomplete; or

(iv) The IND does not contain sufficient information required under §312.23 to assess the risks to subjects of the proposed studies.

(v) The IND is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a

risk or potential risk from use of the investigational drug of reproductive toxicity ( i.e. , affecting reproductive organs) or developmental toxicity ( i.e. , affecting potential offspring). The phrase “women with reproductive potential” does not include pregnant women. For purposes of this paragraph, “life-threatening illnesses or diseases” are defined as “diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.” The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies pertinent only to one gender (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function);

(B) Only in men or women, as long as a study that does not exclude members of the other gender with reproductive potential is being conducted concurrently, has been conducted, or will take place within a reasonable time agreed upon by the agency; or

(C) Only in subjects who do not suffer from the disease or condition for which the drug is being studied.

(2) Clinical hold of a Phase 2 or 3 study under an IND. FDA may place a proposed or ongoing Phase 2 or 3 investigation on clinical hold if it finds that:

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

(ii) The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives.

(3) Clinical hold of an expanded access IND or expanded access protocol . FDA may place an expanded access IND or expanded access protocol on clinical hold under the following conditions:

(i) Final use . FDA may place a proposed expanded access IND or treatment use protocol on clinical hold if it is determined that:

(A) The pertinent criteria in subpart I of this part for permitting the expanded access use to begin are not satisfied; or

(B) The expanded access IND or expanded access protocol does not comply with the requirements for expanded access submissions in subpart I of this part.

(ii) Ongoing use . FDA may place an ongoing expanded access IND or expanded access protocol on clinical hold if it is determined that the pertinent criteria in subpart I of this part for permitting the expanded access are no longer satisfied.

(4) Clinical hold of any study that is not designed to be adequate and well-controlled. FDA may place a proposed or ongoing investigation that is not designed to be adequate and well-controlled on clinical hold if it finds that:

(i) Any of the conditions in paragraph (b)(1) or (b)(2) of this section apply; or

(ii) There is reasonable evidence the investigation that is not designed to be adequate and well-controlled is impeding enrollment in, or otherwise interfering with the conduct or completion of, a study that is designed to be an adequate and well-controlled investigation of the same or another investigational drug; or

(iii) Insufficient quantities of the investigational drug exist to adequately conduct both the investigation that is not designed to be adequate and well-controlled and the investigations that are designed to be adequate and well-controlled; or

(iv) The drug has been studied in one or more adequate and well-controlled investigations that strongly suggest lack of effectiveness; or

(v) Another drug under investigation or approved for the same indication and available to the same patient population has demonstrated a better potential benefit/risk balance; or

(vi) The drug has received marketing approval for the same indication in the same patient population; or

(vii) The sponsor of the study that is designed to be an adequate and well-controlled investigation is not actively pursuing marketing approval of the investigational drug with due diligence; or

(viii) The Commissioner determines that it would not be in the public interest for the study to be conducted or continued. FDA ordinarily intends that clinical holds under paragraphs (b)(4)(ii), (b)(4)(iii) and (b)(4)(v) of this section would only apply to additional enrollment in non-concurrently controlled trials rather than eliminating continued access to individuals already receiving the investigational drug.

(5) Clinical hold of any investigation involving an exception from informed consent under §50.24 of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under §50.24 of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) The pertinent criteria in §50.24 of this chapter for such an investigation to begin or continue are not submitted or not satisfied.

(6) Clinical hold of any investigation involving an exception from informed consent under §50.23(d) of this chapter. FDA may place a proposed or ongoing investigation involving an exception from informed consent under §50.23(d) of this chapter on clinical hold if it is determined that:

(i) Any of the conditions in paragraphs (b)(1) or (b)(2) of this section apply; or

(ii) A determination by the President to waive the prior consent requirement for the administration of an investigational new drug has not been made.

(c) Discussion of deficiency. Whenever FDA concludes that a deficiency exists in a clinical investigation that may be grounds for the imposition of clinical hold FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order.

(d) Imposition of clinical hold. The clinical hold order may be made by telephone or other means of rapid communication or in writing. The clinical hold order will identify the studies under the IND to which the hold applies, and will briefly explain the basis for the action. The clinical hold order will be made by or on behalf of the Division Director with responsibility for review of the IND. As soon as possible, and no more than 30 days after imposition of the clinical hold, the Division Director will provide the sponsor a written explanation of the basis for the hold.

(e) Resumption of clinical investigations. An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has notified the sponsor that the investigation may proceed. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

(f) Appeal. If the sponsor disagrees with the reasons cited for the clinical hold, the sponsor may request reconsideration of the decision in accordance with §312.48.

(g) Conversion of IND on clinical hold to inactive status. If all investigations covered by an IND remain on clinical hold for 1 year or more, the IND may be placed on inactive status by FDA under §312.45.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19477, May 22, 1987; 57 FR 13249, Apr. 15, 1992; 61 FR 51530, Oct. 2, 1996; 63 FR 68678, Dec. 14, 1998; 64 FR 54189, Oct. 5, 1999; 65 FR 34971, June 1, 2000; 74 FR 40942, Aug. 13, 2009]

### **§312.44—Termination.**

(a) General. This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination

action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in §312.42.

(b) Grounds for termination —

(1) Phase 1. FDA may propose to terminate an IND during Phase 1 if it finds that:

- (i) Human subjects would be exposed to an unreasonable and significant risk of illness or injury.
- (ii) The IND does not contain sufficient information required under §312.23 to assess the safety to subjects of the clinical investigations.
- (iii) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for subject safety.
- (iv) The clinical investigations are being conducted in a manner substantially different than that described in the protocols submitted in the IND.
- (v) The drug is being promoted or distributed for commercial purposes not justified by the requirements of the investigation or permitted by §312.7.
- (vi) The IND, or any amendment or report to the IND, contains an untrue statement of a material fact or omits material information required by this part.
- (vii) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of serious and unexpected adverse experiences in accordance with §312.32 or fails to make any other report required under this part.
- (viii) The sponsor fails to submit an accurate annual report of the investigations in accordance with §312.33.
- (ix) The sponsor fails to comply with any other applicable requirement of this part, part 50, or part 56.
- (x) The IND has remained on inactive status for 5 years or more.
- (xi) The sponsor fails to delay a proposed investigation under the IND or to suspend an ongoing investigation that has been placed on clinical hold under §312.42(b)(4).

(2) Phase 2 or 3. FDA may propose to terminate an IND during Phase 2 or Phase 3 if FDA finds that:

- (i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(xi) of this section apply; or
- (ii) The investigational plan or protocol(s) is not reasonable as a bona fide scientific plan to determine whether or not the drug is safe and effective for use; or
- (iii) There is convincing evidence that the drug is not effective for the purpose for which it is being investigated.

(3) FDA may propose to terminate a treatment IND if it finds that:

- (i) Any of the conditions in paragraphs (b)(1)(i) through (x) of this section apply; or
- (ii) Any of the conditions in §312.42(b)(3) apply.

(c) Opportunity for sponsor response.

(1) If FDA proposes to terminate an IND, FDA will notify the sponsor in writing, and invite correction or explanation within a period of 30 days.

(2) On such notification, the sponsor may provide a written explanation or correction or may request a conference with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

(d) Immediate termination of IND. Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by written notice to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of whether the IND should be reinstated.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11579, Mar. 29, 1990; 57 FR 13249, Apr. 15, 1992; 67 FR 9586, Mar. 4, 2002]

### **§312.45—Inactive status.**

(a) If no subjects are entered into clinical studies for a period of 2 years or more under an IND, or if all investigations under an IND remain on clinical hold for 1 year or more, the IND may be placed by FDA on inactive status. This action may be taken by FDA either on request of the sponsor or on FDA's own initiative. If FDA seeks to act on its own initiative under this section, it shall first notify the sponsor in writing of the proposed inactive status. Upon receipt of such notification, the sponsor shall have 30 days to respond as to why the IND should continue to remain active.

(b) If an IND is placed on inactive status, all investigators shall be so notified and all stocks of the drug shall be returned or otherwise disposed of in accordance with §312.59.

(c) A sponsor is not required to submit annual reports to an IND on inactive status. An inactive IND is, however, still in effect for purposes of the public disclosure of data and information under §312.130.

(d) A sponsor who intends to resume clinical investigation under an IND placed on inactive status shall submit a protocol amendment under §312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, the plan shall reference such information. Additional information supporting the proposed investigation, if any, shall be submitted in an information amendment. Notwithstanding the provisions of §312.30, clinical investigations under an IND on inactive status may only resume (1) 30 days after FDA receives the protocol amendment, unless FDA notifies the sponsor that the investigations described in the amendment are subject to a clinical hold under §312.42, or (2) on earlier notification by FDA that the clinical investigations described in the protocol amendment may begin.

(e) An IND that remains on inactive status for 5 years or more may be terminated under §312.44.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

### **§312.47—Meetings.**

(a) General. Meetings between a sponsor and the agency are frequently useful in resolving questions and issues raised during the course of a clinical investigation. FDA encourages such meetings to the extent that they aid in the evaluation of the drug and in the solution of scientific problems concerning the drug, to the extent that FDA's resources permit. The general principle underlying the conduct of such meetings is that there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation. These meetings shall be conducted and documented in accordance with part 10.

(b) "End-of-Phase 2" meetings and meetings held before submission of a marketing application. At specific times during the drug investigation process, meetings between FDA and a sponsor can be especially helpful in minimizing wasteful expenditures of time and money and thus in speeding the

drug development and evaluation process. In particular, FDA has found that meetings at the end of Phase 2 of an investigation (end-of-Phase 2 meetings) are of considerable assistance in planning later studies and that meetings held near completion of Phase 3 and before submission of a marketing application (“pre-NDA” meetings) are helpful in developing methods of presentation and submission of data in the marketing application that facilitate review and allow timely FDA response.

(1) End-of-Phase 2 meetings —

(i) Purpose. The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

(ii) Eligibility for meeting. While the end-of-Phase 2 meeting is designed primarily for IND’s involving new molecular entities or major new uses of marketed drugs, a sponsor of any IND may request and obtain an end-of-Phase 2 meeting.

(iii) Timing. To be most useful to the sponsor, end-of-Phase 2 meetings should be held before major commitments of effort and resources to specific Phase 3 tests are made. The scheduling of an end-of-Phase 2 meeting is not, however, intended to delay the transition of an investigation from Phase 2 to Phase 3.

(iv) Advance information. At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor’s plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. The recommended contents of such a submission are described more fully in FDA Staff Manual Guide 4850.7 that is publicly available under FDA’s public information regulations in part 20.

(v) Conduct of meeting. Arrangements for an end-of-Phase 2 meeting are to be made with the division in FDA’s Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research which is responsible for review of the IND. The meeting will be scheduled by FDA at a time convenient to both FDA and the sponsor. Both the sponsor and FDA may bring consultants to the meeting. The meeting should be directed primarily at establishing agreement between FDA and the sponsor of the overall plan for Phase 3 and the objectives and design of particular studies. The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. Agreements reached at the meeting on these matters will be recorded in minutes of the conference that will be taken by FDA in accordance with §10.65 and provided to the sponsor. The minutes along with any other written material provided to the sponsor will serve as a permanent

record of any agreements reached. Barring a significant scientific development that requires otherwise, studies conducted in accordance with the agreement shall be presumed to be sufficient in objective and design for the purpose of obtaining marketing approval for the drug.

(2) “Pre-NDA” and “pre-BLA” meetings. FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug’s effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA’s reviewing division at least 1 month in advance of the meeting the following information:

- (i) A brief summary of the clinical studies to be submitted in the application.
- (ii) A proposed format for organizing the submission, including methods for presenting the data.
- (iii) Information on the status of needed or ongoing pediatric studies.
- (iv) Any other information for discussion at the meeting.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 63 FR 66669, Dec. 2, 1998; 67 FR 9586, Mar. 4, 2002]

### **§312.48—Dispute resolution.**

(a) General. The Food and Drug Administration is committed to resolving differences between sponsors and FDA reviewing divisions with respect to requirements for IND’s as quickly and amicably as possible through the cooperative exchange of information and views.

(b) Administrative and procedural issues. When administrative or procedural disputes arise, the sponsor should first attempt to resolve the matter with the division in FDA’s Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND, beginning with the consumer safety officer assigned to the application. If the dispute is not resolved, the sponsor may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings and obtaining timely replies to inquiries. Further details on this procedure are contained in FDA Staff Manual Guide 4820.7 that is publicly available under FDA’s public information regulations in part 20.

(c) Scientific and medical disputes.

(1) When scientific or medical disputes arise during the drug investigation process, sponsors should discuss the matter directly with the responsible reviewing officials. If necessary, sponsors may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Requests for such meetings shall be directed to the director of the division in FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research which is responsible for review of the IND. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(2) The "end-of-Phase 2" and "pre-NDA" meetings described in §312.47(b) will also provide a timely forum for discussing and resolving scientific and medical issues on which the sponsor disagrees with the agency.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may rely on, and may bring to any meeting, their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations.

[52 FR 8831, Mar. 19, 1987, as amended at 55 FR 11580, Mar. 29, 1990]



## Subpart D—Responsibilities of Sponsors and Investigators

### §312.50—General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

### §312.52—Transfer of obligations to a contract research organization.

(a) A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization. If all obligations are transferred, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred.

(b) A contract research organization that assumes any obligation of a sponsor shall comply with the specific regulations in this chapter applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to “sponsor” in this part apply to a contract research organization to the extent that it assumes one or more obligations of the sponsor.

### **§312.53—Selecting investigators and monitors.**

(a) Selecting investigators. A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug.

(b) Control of drug. A sponsor shall ship investigational new drugs only to investigators participating in the investigation.

(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A signed investigator statement (Form FDA–1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(A) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(B) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(C) Will personally conduct or supervise the described investigation(s);

(D) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(E) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with §312.64;

(F) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(G) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

(2) Curriculum vitae. A curriculum vitae or other statement of qualifications of the investigator showing the education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation.

(3) Clinical protocol.

(i) For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

(ii) For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

(4) Financial disclosure information. Sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

(d) Selecting monitors. A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

**§312.54—Emergency research under §50.24 of this chapter.**

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under §50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures required by §50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor promptly shall submit to the IND file and to Docket Number 95S–0158 in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IND number.

(b) The sponsor also shall monitor such investigations to identify when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in §50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

[61 FR 51530, Oct. 2, 1996, as amended at 68 FR 24879, May 9, 2003]

**§312.55—Informing investigators.**

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in §312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, 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. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with §312.32.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

**§312.56—Review of ongoing investigations.**

(a) The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA–1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of §312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under §312.32. The sponsor shall make annual reports on the progress of the investigation in accordance with §312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by §312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

### **§312.57—Recordkeeping and record retention.**

(a) A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in §54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, §320.38 or §320.63 of this chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in §320.38.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 58 FR 25926, Apr. 28, 1993; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

### **§312.58—Inspection of sponsor’s records and reports.**

(a) FDA inspection. A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) Controlled substances. If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

### **§312.59—Disposition of unused supply of investigational drug.**

The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with §312.57.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

### **§312.60—General responsibilities of investigators.**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator’s care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51530, Oct. 2, 1996]

**§312.61—Control of the investigational drug.**

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

**§312.62—Investigator recordkeeping and record retention.**

(a) Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under §312.59.

(b) Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 61 FR 57280, Nov. 5, 1996; 67 FR 9586, Mar. 4, 2002]

**§312.64—Investigator reports.**

(a) Progress reports. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under §312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) Safety reports. An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case,

the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

(c) Final report. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(d) Financial disclosure reports. The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 5252, Feb. 2, 1998; 67 FR 9586, Mar. 4, 2002]

### **§312.66—Assurance of IRB review.**

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 67 FR 9586, Mar. 4, 2002]

### **§312.68—Inspection of investigator's records and reports.**

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to §312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

### **§312.69—Handling of controlled substances.**

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

**§312.70—Disqualification of a clinical investigator.**

(a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and

Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the Center will discontinue the disqualification proceeding. If an explanation is offered but not

accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing institutional review boards (IRBs) that the investigator is not eligible to receive test articles under this part. The notification to the investigator, sponsor, and IRBs will provide a statement of basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to the FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor and the reviewing IRBs of the determination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 on the question of whether the IND should be reinstated. The determination that an investigation may not be considered

in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible under paragraph (b) of this section may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990; 62 FR 46876, Sept. 5, 1997; 67 FR 9586, Mar. 4, 2002; 77 FR 25359, Apr. 30, 2012]

## Subpart E—Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Authority: 21 U.S.C. 351, 352, 353, 355, 371; 42 U.S.C. 262.

Source: 53 FR 41523, Oct. 21, 1988, unless otherwise noted.

### §312.80—Purpose.

The purpose of this section is to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated §314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards. The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated. The procedure outlined in this section should be interpreted consistent with that purpose.

### §312.81—Scope.

This section applies to new drug and biological products that are being studied for their safety and effectiveness in treating life-threatening or severely-debilitating diseases.

(a) For purposes of this section, the term “life-threatening” means:

- (1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and
- (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival.

(b) For purposes of this section, the term “severely debilitating” means diseases or conditions that cause major irreversible morbidity.

(c) Sponsors are encouraged to consult with FDA on the applicability of these procedures to specific products.

[53 FR 41523, Oct. 21, 1988, as amended at 64 FR 401, Jan. 5, 1999]

### **§312.82—Early consultation.**

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings.

(a) Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) End-of-phase 1 meetings. When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug’s safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in §312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

[53 FR 41523, Oct. 21, 1988, as amended at 63 FR 66669, Dec. 2, 1998]

**§312.83—Treatment protocols.**

If the preliminary analysis of phase 2 test results appears promising, FDA may ask the sponsor to submit a treatment protocol to be reviewed under the procedures and criteria listed in §§312.305 and 312.320. Such a treatment protocol, if requested and granted, would normally remain in effect while the complete data necessary for a marketing application are being assembled by the sponsor and reviewed by FDA (unless grounds exist for clinical hold of ongoing protocols, as provided in §312.42(b)(3)(ii)).

**§312.84—Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses.**

(a) FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability. As part of this evaluation, consistent with the statement of purpose in §312.80, FDA will consider whether the benefits of the drug outweigh the known and potential risks of the drug and the need to answer remaining questions about risks and benefits of the drug, taking into consideration the severity of the disease and the absence of satisfactory alternative therapy.

(b) In making decisions on whether to grant marketing approval for products that have been the subject of an end-of-phase 1 meeting under §312.82, FDA will usually seek the advice of outside expert scientific consultants or advisory committees. Upon the filing of such a marketing application under §314.101 or part 601 of this chapter, FDA will notify the members of the relevant standing advisory committee of the application's filing and its availability for review.

(c) If FDA concludes that the data presented are not sufficient for marketing approval, FDA will issue a complete response letter under §314.110 of this chapter or the biological product licensing procedures. Such letter, in describing the deficiencies in the application, will address why the results of the research design agreed to under §312.82, or in subsequent meetings, have not provided sufficient evidence for marketing approval. Such letter will also describe any recommendations made by the advisory committee regarding the application.

(d) Marketing applications submitted under the procedures contained in this section will be subject to the requirements and procedures contained in part 314 or part 600 of this chapter, as well as those in this subpart.

[53 FR 41523, Oct. 21, 1988, as amended at 76 FR 13880, Mar 15, 2011]

**§312.85—Phase 4 studies.**

Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses

or schedules of administration than were used in phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

**§312.86—Focused FDA regulatory research.**

At the discretion of the agency, FDA may undertake focused regulatory research on critical rate-limiting aspects of the preclinical, chemical/manufacturing, and clinical phases of drug development and evaluation. When initiated, FDA will undertake such research efforts as a means for meeting a public health need in facilitating the development of therapies to treat life-threatening or severely debilitating illnesses.

**§312.87—Active monitoring of conduct and evaluation of clinical trials.**

For drugs covered under this section, the Commissioner and other agency officials will monitor the progress of the conduct and evaluation of clinical trials and be involved in facilitating their appropriate progress.

**§312.88—Safeguards for patient safety.**

All of the safeguards incorporated within parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. This includes the requirements for informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter). These safeguards further include the review of animal studies prior to initial human testing (§312.23), and the monitoring of adverse drug experiences through the requirements of IND safety reports (§312.32), safety update reports during agency review of a marketing application (§314.50 of this chapter), and postmarketing adverse reaction reporting (§314.80 of this chapter).

## Subpart F—Miscellaneous

### §312.110—Import and export requirements.

(a) Imports. An investigational new drug offered for import into the United States complies with the requirements of this part if it is subject to an IND that is in effect for it under §312.40 and: (1) The consignee in the United States is the sponsor of the IND; (2) the consignee is a qualified investigator named in the IND; or (3) the consignee is the domestic agent of a foreign sponsor, is responsible for the control and distribution of the investigational drug, and the IND identifies the consignee and describes what, if any, actions the consignee will take with respect to the investigational drug.

(b) Exports . An investigational new drug may be exported from the United States for use in a clinical investigation under any of the following conditions:

(1) An IND is in effect for the drug under §312.40, the drug complies with the laws of the country to which it is being exported, and each person who receives the drug is an investigator in a study submitted to and allowed to proceed under the IND; or

(2) The drug has valid marketing authorization in Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or in any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, section 802(b)(1)(A), (f), and (g) of the act, and §1.101 of this chapter; or

(3) The drug is being exported to Australia, Canada, Israel, Japan, New Zealand, Switzerland, South Africa, or to any country in the European Union or the European Economic Area, and complies with the laws of the country to which it is being exported, the applicable provisions of section 802(c), (f), and (g) of the act, and §1.101 of this chapter. Drugs exported under this paragraph that are not the subject of an IND are exempt from the label requirement in §312.6(a); or

(4) Except as provided in paragraph (b)(5) of this section, the person exporting the drug sends a written certification to the Office of International Programs (HFG–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, at the time the drug is first exported and

maintains records documenting compliance with this paragraph. The certification shall describe the drug that is to be exported ( i.e. , trade name (if any), generic name, and dosage form), identify the country or countries to which the drug is to be exported, and affirm that:

- (i) The drug is intended for export;
- (ii) The drug is intended for investigational use in a foreign country;
- (iii) The drug meets the foreign purchaser's or consignee's specifications;
- (iv) The drug is not in conflict with the importing country's laws;
- (v) The outer shipping package is labeled to show that the package is intended for export from the United States;
- (vi) The drug is not sold or offered for sale in the United States;
- (vii) The clinical investigation will be conducted in accordance with §312.120;
- (viii) The drug is manufactured, processed, packaged, and held in substantial conformity with current good manufacturing practices;
- (ix) The drug is not adulterated within the meaning of section 501(a)(1), (a)(2)(A), (a)(3), (c), or (d) of the act;
- (x) The drug does not present an imminent hazard to public health, either in the United States, if the drug were to be reimported, or in the foreign country; and
- (xi) The drug is labeled in accordance with the foreign country's laws.

(5) In the event of a national emergency in a foreign country, where the national emergency necessitates exportation of an investigational new drug, the requirements in paragraph (b)(4) of this section apply as follows:

- (i) Situations where the investigational new drug is to be stockpiled in anticipation of a national emergency . There may be instances where exportation of an investigational new drug is needed so that the drug may be stockpiled and made available for use by the importing country if and when a national emergency arises. In such cases:
  - (A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), and/or (b)(4)(ix) of this section, provided that he or she:

(1) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who may receive the investigational new drug;

(2) Provides a written statement from an authorized official of the importing country's government. The statement must attest that the official agrees with the exporter's statement made under paragraph (b)(5)(i)(A)( 1 ) of this section; explain that the drug is to be stockpiled solely for use of the importing country in a national emergency; and describe the potential national emergency that warrants exportation of the investigational new drug under this provision; and

(3) Provides a written statement showing that the Secretary of Health and Human Services (the Secretary), or his or her designee, agrees with the findings of the authorized official of the importing country's government. Persons who wish to obtain a written statement from the Secretary should direct their requests to Secretary's Operations Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202-619-7870 or by e-mail: HHS.SOC@hhs.gov .

(B) Exportation may not proceed until FDA has authorized exportation of the investigational new drug. FDA may deny authorization if the statements provided under paragraphs (b)(5)(i)(A)( 1 ) or (b)(5)(i)(A)( 2 ) of this section are inadequate or if exportation is contrary to public health.

(ii) Situations where the investigational new drug is to be used for a sudden and immediate national emergency . There may be instances where exportation of an investigational new drug is needed so that the drug may be used in a sudden and immediate national emergency that has developed or is developing. In such cases:

(A) A person may export an investigational new drug under paragraph (b)(4) of this section without making an affirmation with respect to any one or more of paragraphs (b)(4)(i), (b)(4)(iv), (b)(4)(v), (b)(4)(vi), (b)(4)(vii), (b)(4)(viii), (b)(4)(ix), and/or (b)(4)(xi), provided that he or she:

(1) Provides a written statement explaining why compliance with each such paragraph is not feasible or is contrary to the best interests of the individuals who are expected to receive the investigational new drug and

(2) Provides sufficient information from an authorized official of the importing country's government to enable the Secretary, or his or her designee, to decide whether a national emergency has developed or is developing in the importing country, whether the investigational new drug will be used solely for that national emergency, and whether prompt exportation of the investigational new drug is necessary. Persons who wish to obtain a determination from the Secretary should direct their requests to Secretary's Operations

Center, Office of Emergency Operations and Security Programs, Office of Public Health Emergency Preparedness, Office of the Secretary, Department of Health and Human Services, 200 Independence Ave. SW., Washington, DC 20201. Requests may be also be sent by FAX: 202–619–7870 or by e-mail: HHS.SOC@hhs.gov .

(B) Exportation may proceed without prior FDA authorization.

(c) Limitations. Exportation under paragraph (b) of this section may not occur if:

(1) For drugs exported under paragraph (b)(1) of this section, the IND pertaining to the clinical investigation is no longer in effect;

(2) For drugs exported under paragraph (b)(2) of this section, the requirements in section 802(b)(1), (f), or (g) of the act are no longer met;

(3) For drugs exported under paragraph (b)(3) of this section, the requirements in section 802(c), (f), or (g) of the act are no longer met;

(4) For drugs exported under paragraph (b)(4) of this section, the conditions underlying the certification or the statements submitted under paragraph (b)(5) of this section are no longer met; or

(5) For any investigational new drugs under this section, the drug no longer complies with the laws of the importing country.

(d) Insulin and antibiotics . New insulin and antibiotic drug products may be exported for investigational use in accordance with section 801(e)(1) of the act without complying with this section.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 64 FR 401, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002; 70 FR 70729, Nov. 23, 2005]

### **§312.120—Foreign clinical studies not conducted under an IND.**

(a) Acceptance of studies.

(1) FDA will accept as support for an IND or application for marketing approval (an application under section 505 of the act or section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262)) a well-designed and well-conducted foreign clinical study not conducted under an IND, if the following conditions are met:

(i) The study was conducted in accordance with good clinical practice (GCP). For the purposes of this section, GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights,

safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study. GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with those described in §50.23 or §50.24(a) of this chapter, or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects; and

(ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.

(2) Although FDA will not accept as support for an IND or application for marketing approval a study that does not meet the conditions of paragraph (a)(1) of this section, FDA will examine data from such a study.

(3) Marketing approval of a new drug based solely on foreign clinical data is governed by §314.106 of this chapter.

(b) Supporting information. A sponsor or applicant who submits data from a foreign clinical study not conducted under an IND as support for an IND or application for marketing approval must submit to FDA, in addition to information required elsewhere in parts 312, 314, or 601 of this chapter, a description of the actions the sponsor or applicant took to ensure that the research conformed to GCP as described in paragraph (a)(1)(i) of this section. The description is not required to duplicate information already submitted in the IND or application for marketing approval. Instead, the description must provide either the following information or a cross-reference to another section of the submission where the information is located:

(1) The investigator's qualifications;

(2) A description of the research facilities;

(3) A detailed summary of the protocol and results of the study and, should FDA request, case records maintained by the investigator or additional background data such as hospital or other institutional records;

(4) A description of the drug substance and drug product used in the study, including a description of the components, formulation, specifications, and, if available, bioavailability of the specific drug product used in the clinical study;

(5) If the study is intended to support the effectiveness of a drug product, information showing that the study is adequate and well controlled under §314.126 of this chapter;

(6) The name and address of the IEC that reviewed the study and a statement that the IEC meets the definition in §312.3 of this chapter. The sponsor or applicant must maintain records supporting such statement, including records of the names and qualifications of IEC members, and make these records available for agency review upon request;

(7) A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion;

(8) A description of how informed consent was obtained;

(9) A description of what incentives, if any, were provided to subjects to participate in the study;

(10) A description of how the sponsor(s) monitored the study and ensured that the study was carried out consistently with the study protocol; and

(11) A description of how investigators were trained to comply with GCP (as described in paragraph (a)(1)(i) of this section) and to conduct the study in accordance with the study protocol, and a statement on whether written commitments by investigators to comply with GCP and the protocol were obtained. Any signed written commitments by investigators must be maintained by the sponsor or applicant and made available for agency review upon request.

(c) Waivers.

(1) A sponsor or applicant may ask FDA to waive any applicable requirements under paragraphs (a)(1) and (b) of this section. A waiver request may be submitted in an IND or in an information amendment to an IND, or in an application or in an amendment or supplement to an application submitted under part 314 or 601 of this chapter. A waiver request is required to contain at least one of the following:

(i) An explanation why the sponsor's or applicant's compliance with the requirement is unnecessary or cannot be achieved;

(ii) A description of an alternative submission or course of action that satisfies the purpose of the requirement; or

(iii) Other information justifying a waiver.

(2) FDA may grant a waiver if it finds that doing so would be in the interest of the public health.

(d) Records . A sponsor or applicant must retain the records required by this section for a foreign clinical study not conducted under an IND as follows:

(1) If the study is submitted in support of an application for marketing approval, for 2 years after an agency decision on that application;

(2) If the study is submitted in support of an IND but not an application for marketing approval, for 2 years after the submission of the IND.

[73 FR 22815, Apr. 28, 2008]

### **§312.130—Availability for public disclosure of data and information in an IND.**

(a) The existence of an investigational new drug application will not be disclosed by FDA unless it has previously been publicly disclosed or acknowledged.

(b) The availability for public disclosure of all data and information in an investigational new drug application for a new drug will be handled in accordance with the provisions established in §314.430 for the confidentiality of data and information in applications submitted in part 314. The availability for public disclosure of all data and information in an investigational new drug application for a biological product will be governed by the provisions of §§601.50 and 601.51.

(c) Notwithstanding the provisions of §314.430, FDA shall disclose upon request to an individual to whom an investigational new drug has been given a copy of any IND safety report relating to the use in the individual.

(d) The availability of information required to be publicly disclosed for investigations involving an exception from informed consent under §50.24 of this chapter will be handled as follows: Persons wishing to request the publicly disclosable information in the IND that was required to be filed in Docket Number 95S–0158 in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, shall submit a request under the Freedom of Information Act.

[52 FR 8831, Mar. 19, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988, as amended at 61 FR 51530, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999; 68 FR 24879, May 9, 2003]

### **§312.140—Address for correspondence.**

(a) A sponsor must send an initial IND submission to the Center for Drug Evaluation and Research (CDER) or to the Center for Biologics Evaluation and Research (CBER), depending on the Center responsible for regulating the product as follows:

(1) For drug products regulated by CDER. Send the IND submission to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901–B Ammendale Rd., Beltsville, MD 20705–1266; except send an IND submission for an in vivo bioavailability or bioequivalence study in humans to support an abbreviated new drug application to the Office of Generic Drugs (HFD–600), Center for Drug Evaluation and Research, Food and Drug Administration, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

(2) For biological products regulated by CDER . Send the IND submission to the CDER Therapeutic Biological Products Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 12229 Wilkins Ave., Rockville, MD 20852.

(3) For biological products regulated by CBER . Send the IND submission to the Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

(b) On receiving the IND, the responsible Center will inform the sponsor which one of the divisions in CDER or CBER is responsible for the IND. Amendments, reports, and other correspondence relating to matters covered by the IND should be sent to the appropriate center at the address indicated in this section and marked to the attention of the responsible division. The outside wrapper of each submission shall state what is contained in the submission, for example, “IND Application”, “Protocol Amendment”, etc.

(c) All correspondence relating to export of an investigational drug under §312.110(b)(2) shall be submitted to the International Affairs Staff (HFY-50), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

[70 FR 14981, Mar. 24, 2005, as amended at 74 FR 13113, Mar. 26, 2009; 74 FR 55771, Oct. 29, 2009; 75 FR 37295, June 29, 2010]

### **§312.145—Guidance documents.**

(a) FDA has made available guidance documents under §10.115 of this chapter to help you to comply with certain requirements of this part.

(b) The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) maintain lists of guidance documents that apply to the centers’ regulations. The lists are maintained on the Internet and are published annually in the Federal Register. A request for a copy of the CDER list should be directed to the Office of Training and Communications, Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002. A request for a copy of the CBER list should be directed to the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

[65 FR 56479, Sept. 19, 2000, as amended at 74 FR 13113, Mar. 26, 2009]

## Subpart G—Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests

### §312.160—Drugs for investigational use in laboratory research animals or in vitro tests.

(a) Authorization to ship.

(1)(i) A person may ship a drug intended solely for tests in vitro or in animals used only for laboratory research purposes if it is labeled as follows:

***CAUTION: Contains a new drug for investigational use only in laboratory research animals, or for tests in vitro. Not for use in humans.***

(ii) A person may ship a biological product for investigational in vitro diagnostic use that is listed in §312.2(b)(2)(ii) if it is labeled as follows:

***CAUTION: Contains a biological product for investigational in vitro diagnostic tests only.***

(2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for tests in vitro or in animals used only for laboratory research.

(3) A person who ships a drug under paragraph (a) of this section shall maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. Records and reports of data and shipments under paragraph (a)(1)(ii) of this section are to be maintained in accordance with §312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify records required to be maintained under this section.

(b) Termination of authorization to ship. FDA may terminate authorization to ship a drug under this section if it finds that:

(1) The sponsor of the investigation has failed to comply with any of the conditions for shipment established under this section; or

(2) The continuance of the investigation is unsafe or otherwise contrary to the public interest or the drug is used for purposes other than bona fide scientific investigation. FDA will notify the person shipping the drug of its finding and invite immediate correction. If correction is not immediately made, the person shall have an opportunity for a regulatory hearing before FDA pursuant to part 16.

(c) Disposition of unused drug. The person who ships the drug under paragraph (a) of this section shall assure the return of all unused supplies of the drug from individual investigators whenever the investigation discontinues or the investigation is terminated. The person who ships the drug may authorize in writing alternative disposition of unused supplies of the drug provided this alternative disposition does not expose humans to risks from the drug, either directly or indirectly (e.g., through food-producing animals). The shipper shall maintain records of any alternative disposition.

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987. Redesignated at 53 FR 41523, Oct. 21, 1988; 67 FR 9586, Mar. 4, 2002]

## Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)

Source: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571>

An Investigational New Drug Application (IND) is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application.

IND regulations are contained in Title 21, Code of Federal Regulations, Part 312. Copies of the regulations, further guidance regarding IND procedures, and additional forms are available from the FDA Center for Drug Evaluation and Research, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, Maryland 20857, telephone (301) 827-4573 or toll free at 1-888-INFOFDA. In addition, forms, regulations, guidances, and a wide variety of additional information are available online on the FDA Web site. Forms may be accessed directly on the FDA Forms page.

The following instructions address only the administrative aspects of preparing and submitting an IND and are intended primarily to provide assistance to individual Sponsor-Investigator applicants, not pharmaceutical companies.

### Where to Send the Application:

The initial IND submission and each subsequent submission to the IND should be accompanied by a Form FDA 1571 and must be submitted in triplicate (the original and two photocopies are acceptable). Mailing addresses for initial IND submissions are:

#### For a Drug:

Food and Drug Administration  
Center for Drug Evaluation & Research  
Central Document Room  
5901-B Ammendale Road  
Beltsville, Md. 20705-1266

#### For a Therapeutic Biological Product:

Food and Drug Administration  
Center for Drug Evaluation & Research  
Therapeutic Biological Products Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

## Filling Out Form FDA 1571

(The numbers below correspond to the numbered boxes on the Form FDA 1571.)

1. The sponsor is the person who takes responsibility for and initiates a clinical investigation. The sponsor may be a pharmaceutical company, a private or academic organization, or an individual. **A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed.** For administrative reasons, only one individual should be designated as sponsor. If a pharmaceutical company will be supplying the drug, but will not itself be submitting the IND, the company is not the sponsor.
2. The date of submission is the date that the application is mailed to FDA.
3. The address is the address to which written correspondence from FDA should be directed. If this address is a post office box number, a street address must also be provided.
4. The telephone number is the number where the sponsor is usually available during normal working hours. A telephone number must be provided.
5. For name(s) of drug, list the generic name(s) and trade name, if available. Also, state the dosage form(s).
6. If an emergency IND number was previously assigned by FDA, or the Form FDA 1571 is being included with an amendment to the original IND, then that IND number should be entered here; otherwise, the space should be left blank.
7. Self-explanatory.
8. This section is to be completed by pharmaceutical firms that are conducting clinical studies in support of a marketing application. Sponsor-Investigators need not complete this section.
9. It is necessary for the sponsor to submit certain information with an IND (such as manufacturing and controls information, pharmacology and toxicology data, or data from prior human studies) unless that information has previously been submitted to FDA, AND the sponsor of the previously submitted information provides a letter authorizing FDA to refer to the information. In this case, the letter of authorization including the file identification (IND/DMF/NDA number) must be: 1) submitted to the authorizer's application and, 2) included in the initial submission of the new sponsor's IND. The sole exception to this requirement is when a marketed drug is used in the study, without modification to its approved packaging, in which case the marketed drug product must be identified by trade name, established name, dosage form, strength, and lot number.
10. Numbering of submissions is primarily intended for pharmaceutical firms. Sponsor-Investigators do not have to complete this section.

- 11.** For an original IND submission, only the “Initial Investigational New Drug Application (IND)” box should be checked. For subsequent submissions, check ALL the boxes that apply since the submission may contain more than one type of information.

Requests to charge and Treatment Protocols must be submitted separately. Treatment INDs and Treatment Protocols are special cases and are not intended for single patient use. Before checking either of these boxes, the sponsor should be thoroughly familiar with the cited regulations and contact the appropriate FDA reviewing division to discuss the proposed treatment use.

- 12.** For a Sponsor-Investigator IND, items 2, 3, and 4 may be briefly addressed in the cover letter or in a summary. Where the investigational drug is obtained from a supplier in a final dosage form, items 5, 7, 8, and 9 may be referenced if authorization is given by the supplier (see explanation in section 9 above). If the investigational drug is prepared or altered in any way after shipment by the supplier, complete manufacturing (or compounding) and controls information, including information on sterility and pyrogenicity testing for parenteral drugs, must be submitted for that process in Item 7.

Item 6 requires that the protocol be submitted, along with information on the investigators, facilities, and Institutional Review Board (copies of the completed Form FDA 1572 with attachments would suffice for 6 b-d). Item 7 also requires submission of either a claim of categorical exclusion from the requirement to submit an environmental assessment or an environmental assessment (21 CFR 25.15[a]). When claiming a categorical exclusion, the sponsor should include the following statements: “I claim categorical exclusion (under 21 CFR 25.31[e]) for the study(ies) under this IND. To my knowledge, no extraordinary circumstances exist.”

- 13.** This section does not pertain to a Sponsor-Investigator.

- 14-15.** For a pharmaceutical firm, the name of the person responsible for monitoring the conduct of the clinical investigation, and reviewing and evaluating safety information, should be entered. For Sponsor-Investigator INDs, the investigator has this responsibility.

N.B. Certain important commitments that the IND sponsor makes by signing the form FDA 1571 are listed below box 15.

- 16-17.** For an IND sponsored by a pharmaceutical firm or research organization, the name of the sponsor’s authorizing representative would be entered and that individual must sign the form. For a Sponsor-Investigator IND, the Sponsor-Investigator should be named and must sign the form.

- 18-19.** Box 18 and 19 need not be completed if they duplicate boxes 3 and 4.

- 20.** The date here is the date the form is signed by the sponsor.

### **Form FDA 1572:**

Copies of Form FDA 1572 with its attachments may be sent by the Sponsor-Investigator to FDA to satisfy Form FDA 1571, box 12, item 6 b-d. Information can be supplied in the form of attachments (such as a curriculum vitae) rather than entering that information directly onto the form, but this should be so noted under the relevant section numbers.

### **Form FDA 3674:**

The Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) was enacted on September 27, 2007. Title VIII of FDAAA added new Section 402(j) to the Public Health Service Act (42 USC § 282(j)) and expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

Title VIII further requires that, at the time of submission of an application under section 505 of the FDCA, including an Investigational New Drug application, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) numbers. You may use Form FDA 3674, Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank, to comply with the certification requirement. The form may also be found on the FDA Forms page.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of that subsection apply to any clinical trial(s) referenced in your application. Additional information regarding the certification form is available on the FDAAA Certification to Accompany Drug, Biological Product, and Device Applications or Submissions Web page. Additional information regarding the expansion of ClinicalTrials.gov is available at:<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available on the Protocol Registration System Web site.

Please note that FDA has published a draft guidance, Guidance for Sponsors, Industry, Researchers, Investigators, and FDA Staff – Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, 42 U.S.C. § 282(j), Added by Title VIII of the Food and Drug Administration Amendments Acts of 2007. In this guidance, FDA recognizes that certain information and documents submitted to FDA typically bear no relationship to the type of information that Title VIII is designed to capture and that it would not further the purposes of the legislation if a certification were to accompany every type of information or document submitted to the Agency regarding a medical product regulated by FDA. Consequently, FDA identifies in the guidance several types of information and documents that typically need not be accompanied by this certification. For assistance in determining whether your submission of an application under section 505 of the FDCA must be accompanied by a certification, you may consult this guidance.

**FDA Receipt of the IND:**

Upon receipt of the IND by FDA, an IND number will be assigned, and the application will be forwarded to the appropriate reviewing division. The reviewing division will send a letter to the Sponsor-Investigator providing notification of the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA person to whom questions about the application should be directed. Studies shall not be initiated until 30 days after the date of receipt of the IND by FDA unless you receive earlier notification by FDA that studies may begin.

## U.S. Food and Drug Administration

### CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

#### Information on Submitting an Investigational New Drug Application for a Biological Product

Source: <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDProcess/ucm094309.htm>

An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.

The following forms and informational material are provided for assistance in preparing and submitting an IND for a biological product.

1. All Biological IND submissions must be made in triplicate and should be addressed as follows:  
Center for Biologics Evaluation and Research  
HFM-99, Room 200N  
1401 Rockville Pike  
Rockville, MD 20852-1448
2. Emergency Use IND Requests:  
For investigational biological products regulated by CBER, call 301-827-2000.  
For all other investigational drugs, call 301-827-4570.  
After working hours, call FDA's Office of Emergency Operations at 301-443-1240.
3. FDA Form 3674 - Certification of Compliance, under 42 U.S.C. , 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C., 282(j)) (PDF - 847 KB) Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the Public Health Service Act

(PHS Act) by adding section 402(j) (42 U.S.C. 282(j)). The new provisions require additional information to be submitted to the clinical trials data bank (ClinicalTrials.gov), including expanded information on clinical trials and information on the results of clinical trials. One new FDAAA provision, 42 U.S.C. 282(j)(5)(B), requires that a certification accompany human drug, biological, and device product submissions made to FDA. At the time of submission of an application under sections 505, 515, or 520(m) of the FD&C Act (21 U.S.C. 355, 360e, or 360j(m)), or under section 351 of the PHS Act (21 U.S.C. 262), or submission of a report under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), such application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) numbers. FDAAA requires that the certifications be submitted to FDA beginning no later than December 26, 2007.

**Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff:** Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of The Food and Drug Administration Amendments Act of 2007 - 4/21/2008

**FEDERAL REGISTER:** Agency Emergency Processing Under the Office of Management and Budget Review; Certification to Accompany Drug, Biological Product, and Device Applications or Submissions; Correction - 12/26/2007

**FEDERAL REGISTER:** Agency Emergency Processing Under the Office of Management and Budget Review; Certification to Accompany Drug, Biological Product, and Device Applications or Submissions - 12/12/2007

4. Investigational New Drug Application (Form FDA 1571) - Outlines the information required in an IND. All sections on form FDA 1571 must be addressed in the submission. Also, in signing the form, the sponsor agrees to certain important conditions that are summarized just above the section for the sponsor's signature
5. Statement of Investigator (Form FDA 1572) - When this form is completed by each investigator, the original signed copy must be given to the IND sponsor.
6. IND Regulations - Title 21 of the Code of Federal Regulations (CFR), Part 312 (21 CFR 312)
7. Current Good Manufacturing Practice in Manufacturing, Processing, Packaging or Holding of Drugs; General (21 CFR 210)
8. Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR 211)
9. Biological Products: General (21 CFR 600)  
General Biological Products Standards (21 CFR 610)

These regulations include descriptions of the General Safety and Sterility tests that are performed on biological products administered by parenteral routes. The General Safety test is performed primarily as a check on the adequacy of the filling procedure of the final containers and is not intended as a safety test of the product itself. Both bulk and final container sterility tests should be performed as described in Section 610.12. The lot number together with the results of all tests performed on each lot of product should be submitted prior to use in clinical trials.

10. Adequate and Well-controlled Clinical Trials (21 CFR 314.126) - Pertains to studies submitted in support of new drug applications (NDAs) for drugs, but most of the concepts are also relevant to biological products.
11. Informed Consent of Human Subjects (21 CFR 50, Subpart B)
12. Institutional Review Boards (21 CFR 56)
13. Good Laboratory Practices for Nonclinical Laboratory Studies (21 CFR 58)
14. Refer to General Guidances and Guidelines, Points to Consider, and Guidances specific to IND submissions.
15. Good Clinical Practice in FDA-Regulated Clinical Trials
16. SOPP 8201 - Issuance of and Response to Clinical Hold Letters for Investigational New Drug Applications
17. SOPP 8202 - Handling INDs Submitted with Insufficient Copies
18. SOPP 8007 - DCC Binding Procedures for Regulatory Documents
19. Draft Guidance for Industry and Reviewers: Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers
20. Information on the Use of Antivenoms

Information on ordering current and complete copies of the regulations over which FDA has jurisdiction (21 CFR), and how to subscribe to the Federal Register, may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20401, 202-512-0000.

Questions regarding IND submissions may be directed to the Manufacturers Assistance and Technical Training Branch, 800-835-4709 or 301-827-1800.

Web Page Updated: September 07, 2009



# **VI. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - ICH Harmonised Tripartite Guideline for Good Clinical Practice**

**Guidance for Industry  
E6 Good Clinical Practice:  
Consolidated Guidance**

**Additional copies are available from:**

**The Drug Information Branch (HFD-210),  
Center for Drug Evaluation and Research (CDER),**  
5600 Fishers Lane, Rockville, MD 20857  
(Tel) 301-827-4573  
<http://www.fda.gov/cder/guidance/index.htm>

**or**

**Office of Communication, Training, and Manufacturers Assistance (HFM-40)  
Center for Biologics Evaluation and Research (CBER)**  
1401 Rockville Pike, Rockville, MD 20852-1448,  
(Fax) 888-CBERFAX or 301-827-3844  
(Voice Information) 800-835-4709 or 301-827-1800  
<http://www.fda.gov/cber/guidelines.htm>

**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)  
April 1996  
ICH**



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**GUIDANCE FOR INDUSTRY**  
**E6 Good Clinical Practice: Consolidated Guidance**

## INTRODUCTION

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guidance was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries, and the World Health Organization (WHO).

This guidance should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guidance may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.



# 1. GLOSSARY

**1.1—Adverse drug reaction (ADR):** In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

**1.2—Adverse event (AE):** An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

**1.3—Amendment (to the protocol):** See Protocol Amendment.

**1.4—Applicable regulatory requirement(s):** Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where trial is conducted.

**1.5—Approval (in relation to institutional review boards (IRBs)):** The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

**1.6—Audit:** A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were

recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

**1.7—Audit certificate:** A declaration of confirmation by the auditor that an audit has taken place.

**1.8—Audit report:** A written evaluation by the sponsor's auditor of the results of the audit.

**1.9—Audit trail:** Documentation that allows reconstruction of the course of events.

**1.10—Blinding/masking:** A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

**1.11—Case report form (CRF):** A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

**1.12—Clinical trial/study:** Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

**1.13—Clinical Trial/Study Report:** A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guidance for Structure and Content of Clinical Study Reports).

**1.14—Comparator (Product):** An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

**1.15—Compliance (in relation to trials):** Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

**1.16—Confidentiality:** Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

**1.17—Contract:** A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

**1.18—Coordinating Committee:** A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

**1.19—Coordinating Investigator:** An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

**1.20—Contract Research Organization (CRO):** A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor’s trial-related duties and functions.

**1.21—Direct Access:** Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects’ identities and sponsor’s proprietary information.

**1.22—Documentation:** All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

**1.23—Essential Documents:** Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see section 8. “Essential Documents for the Conduct of a Clinical Trial”).

**1.24—Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

**1.25—Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee):** An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

**1.26—Impartial Witness:** A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

**1.27—Independent Ethics Committee (IEC):** An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations, and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance.

**1.28—Informed Consent:** A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

**1.29—Inspection:** The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organization’s (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

**1.30—Institution (medical):** Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

**1.31—Institutional Review Board (IRB):** An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

**1.32—Interim Clinical Trial/Study Report:** A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

**1.33—Investigational Product:** A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

**1.34—Investigator:** A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

**1.35—Investigator/Institution:** An expression meaning “the investigator and/or institution, where required by the applicable regulatory requirements.”

**1.36—Investigator’s Brochure:** A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects (see section 7. “Investigator’s Brochure”).

**1.37—Legally Acceptable Representative:** An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial.

**1.38—Monitoring:** The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

**1.39—Monitoring Report:** A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs.

**1.40—Multicenter Trial:** A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

**1.41—Nonclinical Study:** Biomedical studies not performed on human subjects.

**1.42—Opinion (in relation to Independent Ethics Committee):** The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

**1.43—Original Medical Record:** See 1.52 Source Documents.

**1.44—Protocol:** A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance, the term protocol refers to protocol and protocol amendments.

**1.45—Protocol Amendment:** A written description of a change(s) to or formal clarification of a protocol.

**1.46—Quality Assurance (QA):** All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s).

**1.47—Quality Control (QC):** The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

**1.48—Randomization:** The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

**1.49—Regulatory Authorities:** Bodies having the power to regulate. In the ICH GCP guidance, the expression “Regulatory Authorities” includes the authorities that review submitted clinical data and those that conduct inspections (see section 1.29). These bodies are sometimes referred to as competent authorities.

**1.50—Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR):** Any untoward medical occurrence that at any dose:

Results in death,

Is life-threatening,

Requires inpatient hospitalization or prolongation of existing hospitalization,

Results in persistent or significant disability/incapacity, or

Is a congenital anomaly/birth defect.

(See the ICH Guideline E2A Safety Data Management: Definitions and Standards for Expedited Reporting. [<http://www.ifpma.org/pdfifpma/e2a.pdf>])

**1.51—Source Data:** All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

**1.52—Source Documents:** Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

**1.53—Sponsor:** An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

**1.54—Sponsor-Investigator:** An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency).

The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

**1.55—Standard Operating Procedures (SOPs):** Detailed, written instructions to achieve uniformity of the performance of a specific function.

**1.56—Subinvestigator:** Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

**1.57—Subject/Trial Subject:** An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

**1.58—Subject Identification Code:** A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

**1.59—Trial Site:** The location(s) where trial-related activities are actually conducted.

**1.60—Unexpected Adverse Drug Reaction:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

**1.61—Vulnerable Subjects:** Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

**1.62—Well-being (of the trial subjects):** The physical and mental integrity of the subjects participating in a clinical trial.



## 2. THE PRINCIPLES OF ICH GCP

**2.1**—Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

**2.2**—Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

**2.3**—The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

**2.4**—The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

**2.5**—Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

**2.6**—A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.

**2.7**—The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

**2.8**—Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

**2.9**—Freely given informed consent should be obtained from every subject prior to clinical trial participation.

**2.10**—All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

**2.11**—The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

**2.12**—Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

**2.13**—Systems with procedures that assure the quality of every aspect of the trial should be implemented.

## 3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

### 3.1—Responsibilities.

**3.1.1**—An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

**3.1.2**—The IRB/IEC should obtain the following documents:

Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator’s Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfill its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

Approval/favorable opinion;

Modifications required prior to its approval/favorable opinion;

Disapproval/negative opinion; and

Termination/suspension of any prior approval/favorable opinion.

**3.1.3**—The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

**3.1.4**—The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

**3.1.5**—The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

**3.1.6**—When a nontherapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see sections 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

**3.1.7**—Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see section 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

**3.1.8**—The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

**3.1.9**—The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

### **3.2—Composition, Functions, and Operations.**

**3.2.1**—The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

- (a) At least five members.
- (b) At least one member whose primary area of interest is in a nonscientific area.
- (c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

**3.2.2**—The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

**3.2.3**—An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

**3.2.4**—Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

**3.2.5**—The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

**3.2.6**—An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

### **3.3—Procedures.**

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

**3.3.1**—Determining its composition (names and qualifications of the members) and the authority under which it is established.

**3.3.2**—Scheduling, notifying its members of, and conducting its meetings.

**3.3.3**—Conducting initial and continuing review of trials.

**3.3.4**—Determining the frequency of continuing review, as appropriate.

**3.3.5**—Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

**3.3.6**—Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

**3.3.7**—Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see section 4.5.2).

**3.3.8**—Specifying that the investigator should promptly report to the IRB/IEC:

- (a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see sections 3.3.7, 4.5.2, 4.5.4)

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see section 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

**3.3.9**—Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

**3.4—Records.**

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

## 4. INVESTIGATOR

### 4.1—Investigator’s Qualifications and Agreements.

**4.1.1**—The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

**4.1.2**—The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator’s Brochure, in the product information, and in other information sources provided by the sponsor.

**4.1.3**—The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

**4.1.4**—The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

**4.1.5**—The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

### 4.2— Adequate Resources.

**4.2.1**—The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

**4.2.2**—The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

**4.2.3**—The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

**4.2.4**—The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

### **4.3—Medical Care of Trial Subjects.**

**4.3.1**—A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

**4.3.2**—During and following a subject’s participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

**4.3.3**—It is recommended that the investigator inform the subject’s primary physician about the subject’s participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

**4.3.4**—Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject’s rights.

### **4.4—Communication with IRB/IEC.**

**4.4.1**—Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

**4.4.2**—As part of the investigator’s/institution’s written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator’s Brochure. If the Investigator’s Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator’s Brochure to the IRB/IEC.

**4.4.3**—During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

### **4.5—Compliance with Protocol.**

**4.5.1**—The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

**4.5.2**—The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

**4.5.3**—The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

**4.5.4**—The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- (a) To the IRB/IEC for review and approval/favorable opinion;
- (b) To the sponsor for agreement and, if required;
- (c) To the regulatory authority(ies).

#### **4.6—Investigational Product(s).**

**4.6.1**—Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

**4.6.2**—Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

**4.6.3**—The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

**4.6.4**—The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

**4.6.5**—The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

**4.6.6**—The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

**4.7—Randomization Procedures and Unblinding.**

The investigator should follow the trial’s randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

**4.8—Informed Consent of Trial Subjects.**

**4.8.1**—In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, the investigator should have the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

**4.8.2**—The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form and written information should receive the IRB/IEC’s approval/favorable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

**4.8.3**—Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

**4.8.4**—None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject’s legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

**4.8.5**—The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject’s legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

**4.8.6**—The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject’s legally acceptable representative and the impartial witness, where applicable.

**4.8.7**—Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject’s legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject’s legally acceptable representative.

**4.8.8**—Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion.

**4.8.9**—If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject’s legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative.

**4.8.10**—Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

- (a) That the trial involves research.
- (b) The purpose of the trial.
- (c) The trial treatment(s) and the probability for random assignment to each treatment.
- (d) The trial procedures to be followed, including all invasive procedures.
- (e) The subject’s responsibilities.
- (f) Those aspects of the trial that are experimental.
- (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

**4.8.11**—Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.

During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

**4.8.12**—When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

**4.8.13**—Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

**4.8.14**—Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- (a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
- (b) The foreseeable risks to the subjects are low.
- (c) The negative impact on the subject's well-being is minimized and low.
- (d) The trial is not prohibited by law.
- (e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

**4.8.15**—In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested.

#### **4.9—Records and Reports.**

**4.9.1**—The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

**4.9.2**—Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

**4.9.3**—Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

**4.9.4**—The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see section 8.) and as required by the applicable regulatory requirement(s).The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

**4.9.5**—Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section 5.5.12).

**4.9.6**—The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

**4.9.7**—Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

#### **4.10—Progress Reports.**

**4.10.1**—Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

**4.10.2**—The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see section 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

#### **4.11—Safety Reporting.**

**4.11.1**—All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator’s Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects’ names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

**4.11.2**—Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

**4.11.3**—For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

#### **4.12—Premature Termination or Suspension of a Trial.**

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

**4.12.1**—If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

**4.12.2**—If the sponsor terminates or suspends a trial (see section 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

**4.12.3**—If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

#### **4.13—Final Report(s) by Investigator/Institution.**

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

## 5. SPONSOR

### 5.1—Quality Assurance and Quality Control.

**5.1.1**—The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

**5.1.2**—The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see section 1.21) to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

**5.1.3**—Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

**5.1.4**—Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

### 5.2—Contract Research Organization (CRO).

**5.2.1**—A sponsor may transfer any or all of the sponsor’s trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

**5.2.2**—Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

**5.2.3**—Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

**5.2.4**—All references to a sponsor in this guidance also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

### **5.3—Medical Expertise.**

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

### **5.4—Trial Design.**

**5.4.1**—The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial/study reports.

**5.4.2**—For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see section 6), the ICH Guidance E3: [<http://www.ifpma.org/pdfifpma/e3.pdf>] Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol, and conduct.

### **5.5—Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee.**

**5.5.1**—The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

**5.5.2**—The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

**5.5.3**—When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- (a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).
- (b) Maintain SOPs for using these systems.
- (c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see sections 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

**5.5.4**—If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

**5.5.5**—The sponsor should use an unambiguous subject identification code (see section 1.58) that allows identification of all the data reported for each subject.

**5.5.6**—The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (See section 8. “Essential Documents for the Conduct of a Clinical Trial.”)

**5.5.7**—The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

**5.5.8**—If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

**5.5.9**—If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the appropriate regulatory authorities.

**5.5.10**—Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

**5.5.11**—The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

**5.5.12**—The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/ institution(s) in writing when the trial-related records are no longer needed (see section 4.9.5).

## **5.6—Investigator Selection.**

**5.6.1**—The sponsor is responsible for selecting the investigator(s)/ institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see sections 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor’s responsibility.

**5.6.2**—Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator’s Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

**5.6.3**—The sponsor should obtain the investigator’s/institution’s agreement:

- (a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;
- (b) To comply with procedures for data recording/reporting: and
- (c) To permit monitoring, auditing, and inspection (see section 4.1.4).
- (d) To retain the essential documents that should be in the investigator/institution files (see section 8) until the sponsor informs the investigator/institution these documents are no longer needed (see sections 4.9.4, 4.9.5, and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

## **5.7—Allocation of Duties and Functions.**

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

## **5.8—Compensation to Subjects and Investigators.**

**5.8.1**—If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

**5.8.2**—The sponsor’s policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

**5.8.3**—When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

**5.9—Financing.**

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

**5.10—Notification/Submission to Regulatory Authority(ies).**

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)), should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

**5.11—Confirmation of Review by IRB/IEC.**

**5.11.1**—The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

**5.11.2**—If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

**5.11.3**—The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/ favorable opinion.

**5.12—Information on Investigational Product(s).**

**5.12.1**—When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

**5.12.2**—The sponsor should update the Investigator’s Brochure as significant new information becomes available. (See section 7. “Investigator’s Brochure.”)

**5.13—Manufacturing, Packaging, Labeling, and Coding Investigational Product(s).**

**5.13.1** — sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

**5.13.2**—The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

**5.13.3**—The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

**5.13.4**—In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

**5.13.5**—If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

**5.14—Supplying and Handling Investigational Product(s).**

**5.14.1**—The sponsor is responsible for supplying the investigator(s)/ institution(s) with the investigational product(s).

**5.14.2**—The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

**5.14.3**—The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt,

handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

**5.14.4**—The sponsor should:

- (a) Ensure timely delivery of investigational product(s) to the investigator(s).
- (b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (See section 8. “Essential Documents for the Conduct of a Clinical Trial.”)
- (c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).
- (d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

**5.14.5**—The sponsor should:

- (a) Take steps to ensure that the investigational product(s) are stable over the period of use.
- (b) Maintain sufficient quantities of the investigational product(s) used in the trials to re-confirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

**5.15—Record Access.**

**5.15.1**—The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

**5.15.2**—The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

**5.16—Safety Information.**

**5.16.1**—The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

**5.16.2**—The sponsor should promptly notify all concerned investigator(s)/ institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC’s approval/favorable opinion to continue the trial.

### **5.17—Adverse Drug Reaction Reporting.**

**5.17.1**—The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

**5.17.2**—Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

**5.17.3**—The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

### **5.18—Monitoring.**

**5.18.1**—Purpose. The purposes of trial monitoring are to verify that:

- (a) The rights and well-being of human subjects are protected.
- (b) The reported trial data are accurate, complete, and verifiable from source documents.
- (c) The conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

**5.18.2**—Selection and Qualifications of Monitors

- (a) Monitors should be appointed by the sponsor.
- (b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor’s qualifications should be documented.
- (c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor’s SOPs, GCP, and the applicable regulatory requirement(s).

**5.18.3**—Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

#### 5.18.4—Monitor’s Responsibilities

The monitor(s), in accordance with the sponsor’s requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

- (a) Acting as the main line of communication between the sponsor and the investigator.
- (b) Verifying that the investigator has adequate qualifications and resources (see sections 4.1, 4.2, 5.6) and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.
- (c) Verifying, for the investigational product(s):
  - (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
  - (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
  - (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
  - (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
  - (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor’s authorized procedures.
- (d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
- (e) Verifying that written informed consent was obtained before each subject’s participation in the trial.
- (f) Ensuring that the investigator receives the current Investigator’s Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
- (g) Ensuring that the investigator and the investigator’s trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents. (See section 8. "Essential Documents for the Conduct of a Clinical Trial.")

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

#### **5.18.5—Monitoring Procedures**

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

#### **5.18.6—Monitoring Report**

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor's designated representative.

#### **5.19—Audit.**

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

##### **5.19.1—Purpose**

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

##### **5.19.2—Selection and Qualification of Auditors**

(a) The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

### **5.19.3—Auditing Procedures**

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor’s written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor’s audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports.

Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings.

(e) Where required by applicable law or regulation, the sponsor should provide an audit certificate.

### **5.20—Noncompliance.**

**5.20.1**—Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor’s staff should lead to prompt action by the sponsor to secure compliance.

**5.20.2**—If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator’s/institution’s participation in the trial. When an investigator’s/institution’s participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

### **5.21—Premature Termination or Suspension of a Trial.**

If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

### **5.22—Clinical Trial/Study Reports.**

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial/study reports in marketing applications meet the standards of the ICH Guidance for Structure and

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Content of Clinical Study Reports. (NOTE: The ICH Guidance for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

### **5.23—Multicenter Trials.**

For multicenter trials, the sponsor should ensure that:

**5.23.1**—All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

**5.23.2**—The CRFs are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

**5.23.3**—The responsibilities of the coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

**5.23.4**—All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

**5.23.5**—Communication between investigators is facilitated.



## 6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

### 6.1—General Information.

**6.1.1**—Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

**6.1.2**—Name and address of the sponsor and monitor (if other than the sponsor).

**6.1.3**—Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

**6.1.4**—Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

**6.1.5**—Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

**6.1.6**—Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

**6.1.7**—Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

### 6.2—Background Information.

**6.2.1**—Name and description of the investigational product(s).

**6.2.2**—A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

**6.2.3**—Summary of the known and potential risks and benefits, if any, to human subjects.

**6.2.4**—Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

**6.2.5**—A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

**6.2.6**—Description of the population to be studied.

**6.2.7**—References to literature and data that are relevant to the trial, and that provide background for the trial.

### **6.3—Trial Objectives and Purpose.**

A detailed description of the objectives and the purpose of the trial.

### **6.4—Trial Design.**

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

**6.4.1**—A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

**6.4.2**—A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

**6.4.3**—A description of the measures taken to minimize/avoid bias, including (for example):

(a) Randomization.

(b) Blinding.

**6.4.4**—A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

**6.4.5**—The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

**6.4.6**—A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial, and entire trial.

**6.4.7**—Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

**6.4.8**—Maintenance of trial treatment randomization codes and procedures for breaking codes.

**6.4.9**—The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

### **6.5—Selection and Withdrawal of Subjects.**

**6.5.1**—Subject inclusion criteria.

**6.5.2**—Subject exclusion criteria.

**6.5.3**—Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

- (a) When and how to withdraw subjects from the trial/investigational product treatment.
- (b) The type and timing of the data to be collected for withdrawn subjects.
- (c) Whether and how subjects are to be replaced.
- (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

### **6.6—Treatment of Subjects.**

**6.6.1**—The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

**6.6.2**—Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

**6.6.3**—Procedures for monitoring subject compliance.

### **6.7—Assessment of Efficacy.**

**6.7.1**—Specification of the efficacy parameters.

**6.7.2**—Methods and timing for assessing, recording, and analyzing efficacy parameters.

## **6.8—Assessment of Safety.**

**6.8.1**—Specification of safety parameters.

**6.8.2**—The methods and timing for assessing, recording, and analyzing safety parameters.

**6.8.3**—Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

**6.8.4**—The type and duration of the follow-up of subjects after adverse events.

## **6.9—Statistics.**

**6.9.1**—A description of the statistical methods to be employed, including timing of any planned interim analysis(es).

**6.9.2**—The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified.

Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

**6.9.3**—The level of significance to be used.

**6.9.4**—Criteria for the termination of the trial.

**6.9.5**—Procedure for accounting for missing, unused, and spurious data.

**6.9.6**—Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

**6.9.7**—The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).

## **6.10—Direct Access to Source Data/Documents.**

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

## **6.11—Quality Control and Quality Assurance.**

**6.12—Ethics.**

Description of ethical considerations relating to the trial.

**6.13—Data Handling and Recordkeeping.**

**6.14—Financing and Insurance.**

Financing and insurance if not addressed in a separate agreement.

**6.15—Publication Policy.**

Publication policy, if not addressed in a separate agreement.

**6.16—Supplements.**

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for Structure and Content of Clinical Study Reports. (E3: [<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf>])



## 7. INVESTIGATOR'S BROCHURE

### 7.1—Introduction.

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guidance delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures.

More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator-sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guidance.

## **7.2—General Considerations.**

The Investigator’s Brochure should include:

**7.2.1—Title Page.** This should provide the sponsor’s name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

**7.2.2—Confidentiality Statement.** The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator’s team and the IRB/IEC.

## **7.3—Contents of the Investigator’s Brochure.**

The IB should contain the following sections, each with literature references where appropriate:

**7.3.1—Table of Contents.** An example of the Table of Contents is given in Appendix 2.

**7.3.2—Summary.** A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

**7.3.3—Introduction.** A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

**7.3.4—Physical, Chemical, and Pharmaceutical Properties and Formulation.** A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

### **7.3.5—Nonclinical Studies.**

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

Species tested; Number and sex of animals in each group; Unit dose (e.g., milligram/kilogram (mg/kg)); Dose interval; Route of administration; Duration of dosing; Information on systemic distribution; Duration of post-exposure follow-up; Results, including the following aspects:

Nature and frequency of pharmacological or toxic effects;

Severity or intensity of pharmacological or toxic effects;

Time to onset of effects;

Reversibility of effects;

Duration of effects;

Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

Single dose; Repeated dose; Carcinogenicity; Special studies (e.g., irritancy and sensitization); Reproductive toxicity; Genotoxicity (mutagenicity).

### **7.3.6—Effects in Humans.**

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).

Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

Population subgroups (e.g., gender, age, and impaired organ function). Interactions (e.g., product-product interactions and effects of food).

Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s)).

#### (b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

#### (c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

### 7.3.7—Summary of Data and Guidance for the Investigator.

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the

investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

#### **7.4—Appendix 1 TITLE PAGE OF INVESTIGATOR’S BROCHURE (Example).**

Sponsor’s Name:

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

#### **7.5—Appendix 2 TABLE OF CONTENTS OF INVESTIGATOR’S BROCHURE (Example).**

Confidentiality Statement (optional)

Signature Page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
  - 5.1 Nonclinical Pharmacology
  - 5.2 Pharmacokinetics and Product Metabolism in Animals
  - 5.3 Toxicology
6. Effects in Humans
  - 6.1 Pharmacokinetics and Product Metabolism in Humans
  - 6.2 Safety and Efficacy
  - 6.3 Marketing Experience
7. Summary of Data and Guidance for the Investigator

NB: References on

1. Publications
2. Reports. These references should be found at the end of each chapter. Appendices (if any)

## 8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

### 8.1—Introduction.

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor.

These documents are also the ones that are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial.

A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

**8.2—BEFORE THE CLINICAL PHASE OF THE TRIAL COMMENCES.**

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.2.1</b>	Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
<b>8.2.2</b>	Signed protocol and amendments, if any, and sample case report form (CRF)	To document investigator and sponsor agreement to the protocol/ amendment(s) and CRF	X	X
<b>8.2.3</b>	Information given to trial subject -Informed consent form (including all applicable translations)	To document the informed consent	X	X
	-Any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	-Advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	X	X
<b>8.2.4</b>	Financial aspects of the trial	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.5	Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	Signed agreement between involved parties, e.g.:	To document agreements		
	-Investigator/institution and sponsor		X	X
	-Investigator/institution and CRO		X	X (where required)
	-Sponsor and CRO		X	X
	-Investigator/institution and authority(ies) (Where required)		X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.2.7</b>	<p>Dated, documented, approval/favorable opinion of IRB/IEC of the following:</p> <ul style="list-style-type: none"> <li>-Protocol and any amendments</li> <li>CRF (if applicable)</li> <li>-Informed consent form(s)</li> <li>-Any other written information to be provided to the subject(s)</li> <li>-Advertisement for subject recruitment (if used)</li> <li>-Subject compensation (if any)</li> <li>-Any other documents given approval/favorable opinion</li> </ul>	<p>To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion.</p> <p>To identify the version number and date of the document(s)</p>	X	X
<b>8.2.8</b>	Institutional review board/independent ethics committee composition	To document that the ORB/IEC is constituted in agreement with GCP	X	X (where required)
<b>8.2.9</b>	Regulatory authority(ies) authorization/approval/notification of protocol (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.2.10</b>	Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and subinvestigators	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
<b>8.2.11</b>	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
<b>8.2.12</b>	Medical/laboratory/technical procedures/tests  -Certification or  -Accreditation or  -Established quality control and/or external quality assessment or  -Other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
<b>8.2.13</b>	Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labeling regulations and appropriateness of instructions provided to the subjects	X	X
<b>8.2.14</b>	Instructions for handling of investigational product(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.2.15</b>	Shipping records for investigational product(s) and trial-related materials	To document shipment dates, batch numbers, and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.	X	X
<b>8.2.16</b>	Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational products to be used in the trial		X
<b>8.2.17</b>	Decoding procedures for blinded trials	To document how, in case of an emergency, identify of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
<b>8.2.18</b>	Master randomization list	To document method for randomization of trial population		X (third party if applicable)
<b>8.2.19</b>	Pretrial monitoring report	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
<b>8.2.20</b>	Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and investigator's trial staff (may be combined with 8.2.19)	X	X

**8.3—DURING THE CLINICAL CONDUCT OF THE TRIAL.**

In addition to having the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.3.1</b>	Investigator's Brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
<b>8.3.2</b>	Any revisions to:  -Protocol/amendments(s) and CRF  -Informed consent form  -Any other written information provided to subjects  -Advertisement for subject recruitment (if used)	To document revisions of these trial-related documents that take effect during trial	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.3.3</b>	<p>Dated, documented approval/favorable opinion of institutional review board (IRB)/independent ethics committee (IEC) of the following:</p> <ul style="list-style-type: none"> <li>-Protocol amendment(s)</li> <li>-Revision(s) of:</li> <li>-Informed consent form</li> <li>-Any other written information to be provided to the subject</li> <li>-Advertisement for subject recruitment (if used)</li> <li>-Any other documents given approval/favorable opinion</li> <li>-Continuing review of trial (see section 3.1.4)</li> </ul>	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s)	X	X
<b>8.3.4</b>	<p>Regulatory authority(ies) authorizations/approvals/notifications where required for:</p> <ul style="list-style-type: none"> <li>-Protocol amendment(s) and other documents</li> </ul>	To document compliance with applicable regulatory requirements	X (where required)	X
<b>8.3.5</b>	Curriculum vitae for new investigators) and/or subinvestigators	(See section 8.2.10)	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.3.6</b>	Updates to normal value(s)/range(s) for medical laboratory/technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see section 8.2.11)	X	X
<b>8.3.7</b>	Updates of medical/laboratory/technical procedures/tests  -Certification or -Accreditation or -Established quality control and/or external quality assessment or -Other validation (where required)	To document that tests remain adequate throughout the trial period (see section 8.2.12)	X (where required)	X
<b>8.3.8</b>	Documentation of investigational product(s) and trial-related materials shipment	(See section 8.2.15)	X	X
<b>8.3.9</b>	Certificate(s) of analysis for new batches of investigational products	(See section 8.2.16)		X
<b>8.3.10</b>	Monitoring visit reports	To document site visits by, and findings of, the monitor		X
<b>8.3.11</b>	Relevant communications other than site visits  -Letters -Meeting notes -Notes of telephone calls	To document any agreements of significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.3.12</b>	Signed informed consent forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see section 8.2.3)	X	
<b>8.3.13</b>	Source documents	To document the existence of the subject and substantiate integrity of trial data collected to include original documents related to the trial, to medical treatment, and history of subject	X	
<b>8.3.14</b>	Signed, dated, and completed case report form (CRFs)	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
<b>8.3.15</b>	Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
<b>8.3.16</b>	Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.3.17</b>	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 4.11.2 and 5.16.2	X (where required)	X
<b>8.3.18</b>	Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
<b>8.3.19</b>	Interim or annual reports to IRB/IEC and authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
<b>8.3.20</b>	Subject screening log	To document identification of subjects who entered pretrial screening	X	X (where required)
<b>8.3.21</b>	Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
<b>8.3.22</b>	Subject enrollment log	To document chronological enrollment of subjects by trial number	X	
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.3.23</b>	Investigational product(s) accountability at the site	To document that investigational product(s) have been used according to the protocol	X	X
<b>8.3.24</b>	Signature sheet	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
<b>8.3.25</b>	Record of retained body fluids/tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

#### 8.4—AFTER COMPLETION OR TERMINATION OF THE TRIAL.

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.4.1</b>	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
<b>Continued on next page...</b>				

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
<b>8.4.2</b>	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
<b>8.4.3</b>	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
<b>8.4.4</b>	Audit certificate (if required)	To document that audit was performed (if required) (see section 5.19.3(e))		X
<b>8.4.5</b>	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
<b>8.4.6</b>	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X
<b>8.4.7</b>	Final report by investigator/institution to IRB/IEC where required, and where applicable, to the regulatory authority(ies) (see section 4.13)	To document completion of the trial	X	
<b>8.4.8</b>	Clinical study report (see section 5.22)	To document results and interpretation of trial	X (if applicable)	X



CODE OF FEDERAL REGULATIONS  
TITLE 21  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
PART 812  
INVESTIGATIONAL DEVICE EXEMPTIONS  
\* \* \*  
Revised April 1, 2010  
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## VII. Investigational Devices

### Subpart A—General Provisions

(a) The purpose of this part is to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose. This part provides procedures for the conduct of clinical investigations of devices. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An IDE approved under 812.30 or considered approved under 812.2(b) exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act (the act) and regulations issued thereunder: Misbranding under section 502 of the act, registration, listing, and premarket notification under section 510, performance standards under section 514, premarket approval under section 515, a banned device regulation under section 516, records and reports under section 519, restricted device requirements under section 520(e), good manufacturing practice requirements under section 520(f) except for the requirements found in 820.30, if applicable (unless the sponsor states an intention to comply with these requirements under 812.20(b)(3) or 812.140(b)(4)(v)) and color additive requirements under section 721.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[45 FR 3751, Jan. 18, 1980, as amended at 59 FR 14366, Mar. 28, 1994; 61 FR 52654, Oct. 7, 1996]

#### § 812.2—Applicability.

(a) General. This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section.

(b) Abbreviated requirements. The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with 812.5;

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).

(iv) Complies with the requirements of 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

(2) An investigation of a device other than one subject to paragraph (e) of this section, if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

(c) Exempted investigations. This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) 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.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

(d) Limit on certain exemptions. In the case of class II or class III device described in paragraph (c) (1) or (2) of this section, this part applies beginning on the date stipulated in an FDA regulation or order that calls for the submission of premarket approval applications for an unapproved class III device, or establishes a performance standard for a class II device.

(e) Investigations subject to IND's. A sponsor that, on July 16, 1980, has an effective investigational new drug application (IND) for an investigation of a device shall continue to comply with the requirements of part 312 until 90 days after that date. To continue the investigation after that date, a sponsor shall comply with paragraph (b)(1) of this section, if the device is not a significant risk device, or shall have obtained FDA approval under 812.30 of an IDE application for the investigation of the device.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 46 FR 14340, Feb. 27, 1981; 53 FR 11252, Apr. 6, 1988; 62 FR 4165, Jan. 29, 1997; 62 FR 12096, Mar. 14, 1997]

### § 812.3—Definitions.

(a) Act means the Federal Food, Drug, and Cosmetic Act (sections 201-901, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

(b) Custom device means a device that:

- (1) 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) Is not generally available to, or generally used by, other physicians or dentists;
- (3) Is not generally available in finished form for purchase or for dispensing upon prescription;
- (4) Is not offered for commercial distribution through labeling or advertising; and
- (5) Is intended for use by an individual patient named in the order 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.

(c) FDA means the Food and Drug Administration.

(d) Implant means a device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. FDA may, in order to protect public health, determine that devices placed in subjects for shorter periods are also “implants” for purposes of this part.

(e) Institution means a person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans. The term includes, for example, a hospital, retirement home, confinement facility, academic establishment, and device manufacturer. The term has the same meaning as “facility” in section 520(g) of the act.

(f) Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving subjects and established, operated, and functioning in conformance with part 56. The term has the same meaning as “institutional review committee” in section 520(g) of the act.

(g) Investigational device means a device, including a transitional device, that is the object of an investigation.

(h) Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

(i) Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(j) Monitor, when used as a noun, means an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. Monitor, when used as a verb, means to oversee an investigation.

(k) Noninvasive, when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.

(l) Person includes any individual, partnership, corporation, association, scientific or academic establishment, Government agency or organizational unit of a Government agency, and any other legal entity.

(m) Significant risk device means an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

(n) Sponsor means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

(o) Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

(p) Subject means 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 or disease.

(q) Termination means a discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of an investigation before completion.

(r) Transitional device means a device subject to section 520(l) of the act, that is, a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

(s) Unanticipated adverse device effect means 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.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 48 FR 15622, Apr. 12, 1983]

### **§ 812.5—Labeling of investigational devices.**

(a) Contents. An investigational device or its immediate package shall bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 801.1), the quantity of contents, if appropriate, and the following statement: “CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

(b) Prohibitions. The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

(c) Animal research. An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: “CAUTION—Device for investigational use in laboratory animals or other tests that do not involve human subjects.”

(d) The appropriate FDA Center Director, according to the procedures set forth in 801.128 or 809.11 of this chapter, may grant an exception or alternative to the provisions in paragraphs (a) and (c) of this section, to the extent that these provisions are not explicitly required by statute, for specified lots, batches, or other units of a device that are or will be included in the Strategic National Stockpile.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58842, Sept. 5, 1980; 72 FR 73602, Dec. 28, 2007]

**§ 812.7—Prohibition of promotion and other practices.**

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not:

(a) Promote or test market an investigational device, until after FDA has approved the device for commercial distribution.

(b) Commercialize an investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

(c) Unduly prolong an investigation. If data developed by the investigation indicate in the case of a class III device that premarket approval cannot be justified or in the case of a class II device that it will not comply with an applicable performance standard or an amendment to that standard, the sponsor shall promptly terminate the investigation.

(d) Represent that an investigational device is safe or effective for the purposes for which it is being investigated.

**§ 812.10—Waivers.**

(a) Request. A sponsor may request FDA to waive any requirement of this part. A waiver request, with supporting documentation, may be submitted separately or as part of an application to the address in 812.19.

(b) FDA action. FDA may by letter grant a waiver of any requirement that FDA finds is not required by the act and is unnecessary to protect the rights, safety, or welfare of human subjects.

(c) Effect of request. Any requirement shall continue to apply unless and until FDA waives it.

**§ 812.18—Import and export requirements.**

(a) Imports. In addition to complying with other requirements of this part, a person who imports or offers for importation an investigational device subject to this part shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation, or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation.

(b) Exports. A person exporting an investigational device subject to this part shall obtain FDA's prior approval, as required by section 801(e) of the act or comply with section 802 of the act.

[45 FR 3751, Jan. 18, 1980, as amended at 62 FR 26229, May 13, 1997]

**§ 812.19—Address for IDE correspondence.**

(a) If you are sending an application, supplemental application, report, request for waiver, request for import or export approval, or other correspondence relating to matters covered by this part, you must send the submission to the appropriate address as follows:

(1) For devices regulated by the Center for Devices and Radiological Health, send it to Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center, 10903 New Hampshire Ave., Bldg. 66, rm. G609, Silver Spring, MD 20993-0002.

(2) For devices regulated by the Center for Biologics Evaluation and Research, send it to the Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

(3) For devices regulated by the Center for Drug Evaluation and Research, send it to Central Document Control Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

(b) You must state on the outside wrapper of each submission what the submission is, for example, an “IDE application,” a “supplemental IDE application,” or a “correspondence concerning an IDE (or an IDE application).”

[71 FR 42048, July 25, 2006, as amended at 75 FR 20915, Apr. 22, 2010]

## Subpart B—Application and Administrative Action

### § 812.20—Application.

#### (a) Submission.

(1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under 50.24 of this chapter, or if FDA notifies the sponsor that an application is required for an investigation.

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

(3) A sponsor shall submit three copies of a signed "Application for an Investigational Device Exemption" (IDE application), together with accompanying materials, by registered mail or by hand to the address in 812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted by registered mail or by hand.

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under 50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in 50.24 of this chapter.

#### (b) Contents. An IDE application shall include, in the following order:

(1) The name and address of the sponsor.

- (2) A complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in 812.25(a) through (e) or, in lieu of the summary, the complete plan. The sponsor shall submit to FDA a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them.
  - (3) A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.
  - (4) An example of the agreements to be entered into by all investigators to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement.
  - (5) A certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.
  - (6) A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by each such IRB.
  - (7) The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with paragraph (b)(6) of this section.
  - (8) If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device.
  - (9) A claim for categorical exclusion under 25.30 or 25.34 or an environmental assessment under 25.40.
  - (10) Copies of all labeling for the device.
  - (11) Copies of all forms and informational materials to be provided to subjects to obtain informed consent.
  - (12) Any other relevant information FDA requests for review of the application.
- (c) Additional information. FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under part 16.

(d) Information previously submitted . Information previously submitted to the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research, as applicable, in accordance with this chapter ordinarily need not be resubmitted, but may be incorporated by reference.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8956, Jan. 27, 1981; 50 FR 16669, Apr. 26, 1985; 53 FR 11252, Apr. 6, 1988; 61 FR 51530, Oct. 2, 1996; 62 FR 40600, July 29, 1997; 64 FR 10942, Mar. 8, 1999; 73 FR 49942, Aug. 25, 2008]

### **§ 812.25—Investigational plan.**

The investigational plan shall include, in the following order:

(a) Purpose. The name and intended use of the device and the objectives and duration of the investigation.

(b) Protocol. A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound.

(c) Risk analysis. A description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition.

(d) Description of device. A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.

(e) Monitoring procedures. The sponsor's written procedures for monitoring the investigation and the name and address of any monitor.

(f) Labeling. Copies of all labeling for the device.

(g) Consent materials. Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

(h) IRB information. A list of the names, locations, and chairpersons of all IRB's that have been or will be asked to review the investigation, and a certification of any action taken by any of those IRB's with respect to the investigation.

(i) Other institutions. The name and address of each institution at which a part of the investigation may be conducted that has not been identified in paragraph (h) of this section.

(j) Additional records and reports. A description of records and reports that will be maintained on the investigation in addition to those prescribed in subpart G.

**§ 812.27—Report of prior investigations.**

(a) General. The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.

(b) Specific contents. The report also shall include:

(1) A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.

(2) A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of the safety or effectiveness of the device.

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

[45 FR 3751, Jan. 18, 1980, as amended at 50 FR 7518, Feb. 22, 1985]

**§ 812.30—FDA action on applications.**

(a) Approval or disapproval. FDA will notify the sponsor in writing of the date it receives an application. FDA may approve an investigation as proposed, approve it with modifications, or disapprove it. An investigation may not begin until:

(1) Thirty days after FDA receives the application at the address in 812.19 for the investigation of a device other than a banned device, unless FDA notifies the sponsor that the investigation may not begin; or

(2) FDA approves, by order, an IDE for the investigation.

(b) Grounds for disapproval or withdrawal. FDA may disapprove or withdraw approval of an application if FDA finds that:

(1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA.

(2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.

(3) The sponsor fails to respond to a request for additional information within the time prescribed by FDA.

(4) There is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.

(5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:

(i) The report of prior investigations or the investigational plan;

(ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device; or

(iii) Monitoring and review of the investigation.

(c) Notice of disapproval or withdrawal. If FDA disapproves an application or proposes to withdraw approval of an application, FDA will notify the sponsor in writing.

(1) A disapproval order will contain a complete statement of the reasons for disapproval and a statement that the sponsor has an opportunity to request a hearing under part 16.

(2) A notice of a proposed withdrawal of approval will contain a complete statement of the reasons for withdrawal and a statement that the sponsor has an opportunity to request a hearing under part 16. FDA will provide the opportunity for hearing before withdrawal of approval, unless FDA determines in the notice that continuation of testing under the exemption will result in an unreasonable risk to the public health and orders withdrawal of approval before any hearing.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58842, Sept. 5, 1980]

### **§ 812.35—Supplemental applications.**

(a) Changes in investigational plan

(1) Changes requiring prior approval. Except as described in paragraphs (a)(2) through (a)(4) of this section, a sponsor must obtain approval of a supplemental application under 812.30(a), and IRB approval when appropriate (see 56.110 and 56.111 of this chapter), prior to implementing a change to an investigational plan. If a sponsor intends to conduct an investigation that involves an exception to informed consent under 50.24 of this chapter, the sponsor shall submit a separate investigational device exemption (IDE) application in accordance with 812.20(a).

(2) Changes effected for emergency use. The requirements of paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply in the case of a deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see 812.150(a)(4)).

(3) Changes effected with notice to FDA within 5 days. A sponsor may make certain changes without prior approval of a supplemental application under paragraph (a)(1) of this section if the sponsor determines that these changes meet the criteria described in paragraphs (a)(3)(i) and (a)(3)(ii) of this section, on the basis of credible information defined in paragraph (a)(3)(iii) of this section, and the sponsor provides notice to FDA within 5-working days of making these changes.

(i) Developmental changes. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to developmental changes in the device (including manufacturing changes) that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

(ii) Changes to clinical protocol. The requirements in paragraph (a)(1) of this section regarding FDA approval of a supplement do not apply to changes to clinical protocols that do not affect:

(A) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;

(B) The scientific soundness of the investigational plan; or

(C) The rights, safety, or welfare of the human subjects involved in the investigation.

(iii) Definition of credible information.

(A) Credible information to support developmental changes in the device (including manufacturing changes) includes data generated under the design control procedures of 820.30, preclinical/animal testing, peer reviewed published literature, or other reliable information such as clinical information gathered during a trial or marketing.

(B) Credible information to support changes to clinical protocols is defined as the sponsor's documentation supporting the conclusion that a change does not have a significant impact on the study design or planned statistical analysis, and that the change does not affect the rights, safety, or welfare of the subjects. Documentation shall include information such as peer reviewed published literature, the recommendation of the clinical investigator(s), and/or the data gathered during the clinical trial or marketing.

(iv) Notice of IDE change. Changes meeting the criteria in paragraphs (a)(3)(i) and (a)(3)(ii) of this section that are supported by credible information as defined in paragraph (a)(3)(iii) of this section may be made without prior FDA approval if the sponsor submits a notice of the change to the IDE not later than 5-working days after making the change. Changes to devices are deemed to occur on the date the device, manufactured incorporating the design or manufacturing change, is distributed to the investigator(s). Changes to a clinical protocol are deemed to occur when a clinical investigator is notified by the sponsor that the change should be implemented in the protocol or, for sponsor-investigator studies, when a sponsor-investigator incorporates the change in the protocol. Such notices shall be identified as a “notice of IDE change.”

(A) For a developmental or manufacturing change to the device, the notice shall include a summary of the relevant information gathered during the course of the investigation upon which the change was based; a description of the change to the device or manufacturing process (cross-referenced to the appropriate sections of the original device description or manufacturing process); and, if design controls were used to assess the change, a statement that no new risks were identified by appropriate risk analysis and that the verification and validation testing, as appropriate, demonstrated that the design outputs met the design input requirements. If another method of assessment was used, the notice shall include a summary of the information which served as the credible information supporting the change.

(B) For a protocol change, the notice shall include a description of the change (cross-referenced to the appropriate sections of the original protocol); an assessment supporting the conclusion that the change does not have a significant impact on the study design or planned statistical analysis; and a summary of the information that served as the credible information supporting the sponsor’s determination that the change does not affect the rights, safety, or welfare of the subjects.

(4) Changes submitted in annual report. The requirements of paragraph (a)(1) of this section do not apply to minor changes to the purpose of the study, risk analysis, monitoring procedures, labeling, informed consent materials, and IRB information that do not affect:

- (i) The validity of the data or information resulting from the completion of the approved protocol, or the relationship of likely patient risk to benefit relied upon to approve the protocol;
- (ii) The scientific soundness of the investigational plan; or
- (iii) The rights, safety, or welfare of the human subjects involved in the investigation. Such changes shall be reported in the annual progress report for the IDE, under 812.150(b)(5).

(b) IRB approval for new facilities. A sponsor shall submit to FDA a certification of any IRB approval of an investigation or a part of an investigation not included in the IDE application. If the investigation is otherwise unchanged, the supplemental application shall consist of an updating of the information required by 812.20(b) and (c) and a description of any modifications in the investigational plan required by the IRB as a condition of approval. A certification of IRB approval need not be included in the initial submission of the supplemental application, and such certification is

not a precondition for agency consideration of the application. Nevertheless, a sponsor may not begin a part of an investigation at a facility until the IRB has approved the investigation, FDA has received the certification of IRB approval, and FDA, under 812.30(a), has approved the supplemental application relating to that part of the investigation (see 56.103(a)).

[50 FR 25909, June 24, 1985; 50 FR 28932, July 17, 1985, as amended at 61 FR 51531, Oct. 2, 1996; 63 FR 64625, Nov. 23, 1998]

### **§ 812.36—Treatment use of an investigational device.**

(a) General. A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment investigational device exemption (IDE). The purpose of this section is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials. For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For purposes of this section, "treatment use" of a device includes the use of a device for diagnostic purposes.

(b) Criteria. FDA shall consider the use of an investigational device under a treatment IDE if:

- (1) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
- (2) There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population;
- (3) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; and
- (4) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

(c) Applications for treatment use.

(1) A treatment IDE application shall include, in the following order:

- (i) The name, address, and telephone number of the sponsor of the treatment IDE;
- (ii) The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;
- (iii) An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments;
- (iv) A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk;
- (v) Written procedures for monitoring the treatment use and the name and address of the monitor;
- (vi) Instructions for use for the device and all other labeling as required under 812.5(a) and (b);
- (vii) Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDE's may be incorporated by reference to support the treatment use;
- (viii) A statement of the sponsor's commitment to meet all applicable responsibilities under this part and part 56 of this chapter and to ensure compliance of all participating investigators with the informed consent requirements of part 50 of this chapter;
- (ix) An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
- (x) If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

(2) A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under this part and parts 50 and 56 of this chapter.

(d) FDA action on treatment IDE applications

(1) Approval of treatment IDE's. Treatment use may begin 30 days after FDA receives the treatment IDE submission at the address specified in 812.19, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

(2) Disapproval or withdrawal of approval of treatment IDE's. FDA may disapprove or withdraw approval of a treatment IDE if:

(i) The criteria specified in 812.36(b) are not met or the treatment IDE does not contain the information required in 812.36(c);

(ii) FDA determines that any of the grounds for disapproval or withdrawal of approval listed in 812.30(b)(1) through (b)(5) apply;

(iii) The device is intended for a serious disease or condition and there is insufficient evidence of safety and effectiveness to support such use;

(iv) The device is intended for an immediately life-threatening disease or condition and the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the device:

(A) May be effective for its intended use in its intended population; or

(B) Would not expose the patients to whom the device is to be administered to an unreasonable and significant additional risk of illness or injury;

(v) There is reasonable evidence that the treatment use is impeding enrollment in, or otherwise interfering with the conduct or completion of, a controlled investigation of the same or another investigational device;

(vi) The device has received marketing approval/clearance or a comparable device or therapy becomes available to treat or diagnose the same indication in the same patient population for which the investigational device is being used;

(vii) The sponsor of the controlled clinical trial is not pursuing marketing approval/clearance with due diligence;

(viii) Approval of the IDE for the controlled clinical investigation of the device has been withdrawn; or

(ix) The clinical investigator(s) named in the treatment IDE are not qualified by reason of their scientific training and/or experience to use the investigational device for the intended treatment use.

(3) Notice of disapproval or withdrawal. If FDA disapproves or proposes to withdraw approval of a treatment IDE, FDA will follow the procedures set forth in 812.30(c).

(e) Safeguards. Treatment use of an investigational device is conditioned upon the sponsor and investigators complying with the safeguards of the IDE process and the regulations governing informed consent (part 50 of this chapter) and institutional review boards (part 56 of this chapter).

(f) Reporting requirements. The sponsor of a treatment IDE shall submit progress reports on a semi-annual basis to all reviewing IRB's and FDA until the filing of a marketing application. These reports shall be based on the period of time since initial approval of the treatment IDE and shall include the number of patients treated with the device under the treatment IDE, the names of the investigators participating in the treatment IDE, and a brief description of the sponsor's efforts to pursue marketing approval/clearance of the device. Upon filing of a marketing application, progress reports shall be submitted annually in accordance with 812.150(b)(5). The sponsor of a treatment IDE is responsible for submitting all other reports required under 812.150.

[62 FR 48947, Sept. 18, 1997]

### **§ 812.38—Confidentiality of data and information.**

(a) Existence of IDE. FDA will not disclose the existence of an IDE unless its existence has previously been publicly disclosed or acknowledged, until FDA approves an application for premarket approval of the device subject to the IDE; or a notice of completion of a product development protocol for the device has become effective.

(b) Availability of summaries or data.

(1) FDA will make publicly available, upon request, a detailed summary of information concerning the safety and effectiveness of the device that was the basis for an order approving, disapproving, or withdrawing approval of an application for an IDE for a banned device. The summary shall include information on any adverse effect on health caused by the device.

(2) If a device is a banned device or if the existence of an IDE has been publicly disclosed or acknowledged, data or information contained in the file is not available for public disclosure before approval of an application for premarket approval or the effective date of a notice of completion of a product development protocol except as provided in this section. FDA may, in its discretion, disclose a summary of selected portions of the safety and effectiveness data, that is, clinical, animal, or laboratory studies and tests of the device, for public consideration of a specific pending issue.

(3) If the existence of an IDE file has not been publicly disclosed or acknowledged, no data or information in the file are available for public disclosure except as provided in paragraphs (b)(1) and (c) of this section.

(4) Notwithstanding paragraph (b)(2) of this section, FDA will make available to the public, upon request, the information in the IDE that was required to be filed in Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, for investigations involving an exception from informed consent under 50.24 of this chapter. Persons wishing to request this information shall submit a request under the Freedom of Information Act.

(c) Reports of adverse effects. Upon request or on its own initiative, FDA shall disclose to an individual on whom an investigational device has been used a copy of a report of adverse device effects relating to that use.

(d) Other rules. Except as otherwise provided in this section, the availability for public disclosure of data and information in an IDE file shall be handled in accordance with 814.9.

[45 FR 3751, Jan. 18, 1980, as amended at 53 FR 11253, Apr. 6, 1988; 61 FR 51531, Oct. 2, 1996]

## Subpart C—Responsibilities of Sponsors

### § 812.40—General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.

### § 812.42—FDA and IRB approval.

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

[46 FR 8957, Jan. 27, 1981]

### § 812.43—Selecting investigators and monitors.

(a) Selecting investigators. A sponsor shall select investigators qualified by training and experience to investigate the device.

(b) Control of device. A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.

(c) Obtaining agreements. A sponsor shall obtain from each participating investigator a signed agreement that includes:

- (1) The investigator's curriculum vitae.

(2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.

(3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.

(4) A statement of the investigator's commitment to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

(5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.

(d) Selecting monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.

[45 FR 3751, Jan. 18, 1980, as amended at 63 FR 5253, Feb. 2, 1998]

#### **§ 812.45—Informing investigators.**

A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.

#### **§ 812.46—Monitoring investigations.**

(a) Securing compliance. A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

(b) Unanticipated adverse device effects.

(1) A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.

(2) A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.

(c) Resumption of terminated studies. If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of this section, FDA approval.

**§ 812.47—Emergency research under 50.24 of this chapter.**

(a) The sponsor shall monitor the progress of all investigations involving an exception from informed consent under 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures under 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor shall promptly submit to the IDE file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IDE number.

(b) The sponsor also shall monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRB's that are asked to review this or a substantially equivalent investigation.

[61 FR 51531, Oct. 2, 1996, as amended at 64 FR 10943, Mar. 8, 1999]



## Subpart D—IRB Review and Approval

### § 812.60—IRB composition, duties, and functions.

An IRB reviewing and approving investigations under this part shall comply with the requirements of part 56 in all respects, including its composition, duties, and functions.

[46 FR 8957, Jan. 27, 1981]

### § 812.62—IRB approval.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all investigations covered by this part.

(b) If no IRB exists or if FDA finds that an IRB's review is inadequate, a sponsor may submit an application to FDA.

[46 FR 8957, Jan. 27, 1981]

### § 812.64—IRB's continuing review.

The IRB shall conduct its continuing review of an investigation in accordance with part 56.

[46 FR 8957, Jan. 27, 1981]

### § 812.65 [Reserved]

**§ 812.66—Significant risk device determinations.**

If an IRB determines that an investigation, presented for approval under 812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. A sponsor may not begin the investigation except as provided in 812.30(a).

[46 FR 8957, Jan. 27, 1981]

## Subpart E—Responsibilities of Investigators

### § 812.100—General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G.

[45 FR 3751, Jan. 18, 1980, as amended at 46 FR 8957, Jan. 27, 1981]

### § 812.110—Specific responsibilities of investigators.

(a) Awaiting approval. An investigator may determine whether potential subjects would be interested in participating in an investigation, but 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.

(b) Compliance. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

(c) Supervising device use. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.

(d) Financial disclosure. A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

(e) Disposing of device. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

[45 FR 3751, Jan. 18, 1980, as amended at 63 FR 5253, Feb. 2, 1998]

### **§ 812.119—Disqualification of a clinical investigator.**

(a) If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted false information either to the sponsor of the investigation or in any required report, the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, or the Center for Drug Evaluation and Research will furnish the investigator written notice of the matter under complaint and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered and accepted by the applicable Center, the disqualification process will be terminated. If an explanation is offered but not accepted by the Center, the investigator will be given an opportunity for a regulatory hearing under part 16 of this chapter on the question of whether the investigator is entitled to receive test articles under this part and eligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has deliberately or repeatedly submitted false information either to the sponsor of the investigation or in any required report, the Commissioner will notify the investigator, the sponsor of any investigation in which the investigator has been named as a participant, and the reviewing IRB that the investigator is not entitled to receive test articles under this part. The notification to the investigator, sponsor and IRBs will provide a statement of the basis for such determination. The notification also will explain that an investigator determined to be ineligible to receive test articles under this part will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, including drugs, biologics, devices, new animal drugs, foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, and tobacco products.

(c) Each application or submission to FDA under the provisions of this chapter containing data reported by an investigator who has been determined to be ineligible to receive FDA-regulated test articles is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of an investigation or essential to the clearance or approval of a marketing application, or essential to the continued marketing of an FDA-regulated product.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing under part 16 of this chapter. If a danger to the public health exists, however, the Commissioner shall terminate the IDE immediately and notify the sponsor and the reviewing IRBs of the termination. In such case, the sponsor shall have an opportunity for a regulatory hearing before FDA under part 16 of this chapter on the question of whether the IDE should be reinstated. The determination that an investigation may not be considered in support of a research or marketing application or a notification or petition submission does not, however, relieve the sponsor of any obligation under any other applicable regulation to submit to FDA the results of the investigation.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued clearance or approval of the marketing application for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval or rescind clearance of the medical device in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational devices may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ all test articles, and will conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA, solely in compliance with the applicable provisions of this chapter.

[62 FR 12096, Mar. 14, 1997, as amended at 71 FR 76902, Dec. 22, 2006; 77 FR 25360, April 30, 2012]



## Subpart F—[Reserved]

## Subpart G—Records and Reports

### § 812.140—Records.

(a) Investigator records. A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

(1) All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

(ii) The names of all persons who received, used, or disposed of each device.

(iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

(3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:

(i) Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(ii) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon

entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

(iii) A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

(4) The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

(5) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

(b) Sponsor records. A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:

(1) All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.

(2) Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

(3) Signed investigator agreements including the financial disclosure information required to be collected under 812.43(c)(5) in accordance with part 54 of this chapter.

(4) For each investigation subject to 812.2(b)(1) of a device other than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:

(i) The name and intended use of the device and the objectives of the investigation;

(ii) A brief explanation of why the device is not a significant risk device:

(iii) The name and address of each investigator:

(iv) The name and address of each IRB that has reviewed the investigation:

(v) A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and

(vi) Any other information required by FDA.

(5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints and

(6) Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

(c) IRB records. An IRB shall maintain records in accordance with part 56 of this chapter.

(d) Retention period. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

(e) Records custody. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 46 FR 8957, Jan. 27, 1981; 61 FR 57280, Nov. 5, 1996; 63 FR 5253, Feb. 2, 1998]

### **§ 812.145—Inspections.**

(a) Entry and inspection. A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

(b) Records inspection. A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

(c) Records identifying subjects. An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

## § 812.150—Reports.

(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.

(5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) Sponsor reports. A sponsor shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) **Withdrawal of IRB approval.** A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) **Withdrawal of FDA approval.** A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) **Current investigator list.** A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

(5) **Progress reports.** At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with 812.36(f) and annual reports in accordance with this section.

(6) **Recall and device disposition.** A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) **Final report.** In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) **Informed consent.** A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) **Significant risk device determinations.** If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) **Other.** A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 48 FR 15622, Apr. 12, 1983; 62 FR 48948, Sept. 18, 1997]

Authority: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 372, 374, 379e, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b-263n.

Source: 45 FR 3751, Jan. 18, 1980, unless otherwise noted.



## VIII. USEFUL INTERNET SITES

Please note that the web addresses provided are accurate as of April 6, 2015. The Division of Microbiology and Infectious Disease (DMID) will update these web addresses on a regular basis, but acknowledges the web addresses listed below are subject to change.

### HOMEPAGES

#### **National Institutes of Health (NIH)**

<http://www.nih.gov/>

#### **NIH Human Research Protections Program (HRPP)**

<http://ohsr.od.nih.gov/OHSR/index.php>

#### **Grants and Funding, Office of Extramural**

**Research** <http://grants.nih.gov/grants/oer.htm>

#### **National Institute of Allergy and Infectious Diseases (NIAID)**

<http://www.niaid.nih.gov/>

#### **Division of Microbiology and Infectious Diseases (DMID), NIAID**

<http://www.niaid.nih.gov/about/organization/dmid/>

#### **DHHS Office for Human Research Protections (OHRP)**

<http://www.hhs.gov/ohrp/>

#### **U.S. Food and Drug Administration (FDA)**

<http://www.fda.gov/>

#### **FDA Information for Health Professionals**

<http://www.fda.gov/ForHealthProfessionals/default.htm>

**FDA Guidance, Compliance and Regulatory Information (Biologics)**

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

**FDA Guidance, Compliance and Regulatory Information (Drugs)** [http://](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation)

[www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation)

**International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topics and Guidelines**

<http://www.ich.org/products/guidelines.html>

**US ARMY Medical Research and Materiel Command Home Page Human Subjects Protection and Regulatory Divisions— “Regulatory Compliance and Quality”**

<https://mrmc-www.army.mil/>

**Navy Medical Research Center IRB**

<http://www.med.navy.mil/>

**Centers for Disease Control and Prevention (CDC) Human Participant Protection**

<http://www.cdc.gov/od/science/integrity/hrpo/>

**World Health Organization (WHO)**

<http://www.who.int/>

**Pan American Health Organization (PAHO)**

<http://www.paho.org/>

**European Forum for Good Clinical Practice**

<http://www.efgcp.eu/>

**Federal Register**

<http://www.gpoaccess.gov/cfr/index.html>

**21 CFR Database**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm>

**PROTECTION OF HUMAN SUBJECTS PARTICIPATING IN CLINICAL RESEARCH**

**Belmont Report**

<http://www.hhs.gov/ohrp/policy/belmont.html>

**Declaration of Helsinki (2013)**

<http://www.wma.net/en/30publications/10policies/b3/index.html>

**45CFR46-Human Subjects Protection**

<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

**Human Subject Regulations Decision Charts**

<http://www.hhs.gov/ohrp/policy/checklists/decisioncharts.html>

**NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects**

<http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

**National Institutes of Health (NIH) Guidelines on the Inclusion of Women and Minorities as Participants in Research Involving Human Subjects - Policy Implementation Page**

[http://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](http://grants.nih.gov/grants/funding/women_min/women_min.htm)

**FDA's Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) Initiative**

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm228722.htm>

**World Wide Web Sites of Interest for Human Subject Protection Information**

<http://www.fda.gov/ForHealthProfessionals/default.htm>

**FDA Information Sheets: Guidance for Running Clinical Trials and Human Subject Protection**

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

**CLINICAL RESEARCH****NIAID: A Patient's Guide to Clinical Trials**

<http://www.niaid.nih.gov/Volunteer/Pages/clinicalTrials.aspx>

**DHHS: Office for Human Research**

**Protections (OHRP)** [www.hhs.gov/ohrp/](http://www.hhs.gov/ohrp/)

**Frequently Asked Questions (FAQ) for "Certificates of Confidentiality"**

<http://grants.nih.gov/grants/policy/coc/faqs.htm>

**OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events"**

<http://www.hhs.gov/ohrp/policy/advevntguid.html>

**OHRP - Guidance on Research Involving Coded Private Information or Biological Specimens**

<http://www.hhs.gov/ohrp/policy/cdebiol.html>

**FDA Good Clinical Practice (ICH E6)**

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf>

**DMID Toxicity Tables**

<http://www.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/Pages/pharma.aspx>

**CBER Guidances/Guidelines**

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

**CBER Proposed/Final Rules**

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

**Guidance on Research Involving Coded Private Information or Biological Specimens**

<http://www.hhs.gov/ohrp/policy/cdebiol.html>

**FDA INVESTIGATIONAL NEW DRUG APPLICATION (IND)**

**21CFR312—INVESTIGATIONAL NEW DRUG APPLICATION.**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312>

**FDA Import Export Guidance Documents**

<http://www.fda.gov/RegulatoryInformation/Guidances/UCM122048>

**INSTITUTIONAL REVIEW BOARD/ETHICALCOMMITTEE (IRB/EC)**

**21CFR56-Institutional Review Boards**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=56>

**FDA IRB Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators**

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126425.htm>

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**Exempt Research and Research That May Undergo Expedited Review**

<http://www.hhs.gov/ohrp/policy/hcdc95-02.html>

**Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure**

<http://www.hhs.gov/ohrp/policy/expedited98.html>

**IRB Review of Applications for HHS Support**

<http://www.hhs.gov/ohrp/policy/aplrev.html>

**INFORMED CONSENT PROCESS**

**21CFR50-FDA Informed Consent Regulations**

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRsearch.cfm?CFRPart=50>

**Tips on Informed Consent**

<http://www.hhs.gov/ohrp/policy/ictips.html>

**NCI Consent Documents and Guidance**

<http://www.cancer.gov/clinicaltrials/conducting/informed-consent-guide/page3>

**DMID Informed Consent Documents and Guidance**

<http://www.niaid.nih.gov/about/organization/dmid>

**TRAINING IN HUMAN SUBJECTS PROTECTIONS AND GCP**

**NIAID GCP Training**

<https://gcplearningcenter.niaid.nih.gov/Pages/default.aspx>

**NIH Extramural HSP**

<http://phrp.nihtraining.com/users/login.php>



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