HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL & IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: SOP 15 v.2

SOP Title: Research Regulated by the Food and Drug Administration (FDA): General Procedures for Both IND and IDE Applications

Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB Chairs, IRB Administrators, Protocol Navigators

Revision Approval: Michael Gottesman 10/1/13

Deputy Director for Intramural Research **Date**

Revision Implementation date: 10-1-2013

Materials Superseded: SOP 15, dated 6/27/2013

SOP 15 RESEARCH REGULATED BY THE FOOD AND DRUG ADMINISTRATION (FDA): GENERAL PROCEDURES FOR BOTH IND AND IDE APPLICATIONS

TABLE OF CONTENTS

15.1 DEFINITIONS AND LINKS TO WEBSITES 1
15.2 PURPOSE 1
15.3 POLICY 1
15.4 RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR (PI) 2
15.4.1 GENERAL RESPONSIBILITIES AND COMMUNICATION WITH THE IRB 2
15.4.2. INVESTIGATOR QUALIFICATIONS AND SUPERVISORY RESPONSIBILITIES 4
15.4.3. ADEQUATE RESOURCES, INCLUDING QUALIFIED STAFF, TO CONDUCT THE RESEARCH 5
15.4.4. MEDICAL CARE OF RESEARCH SUBJECTS 5
15.4.5. WITHDRAWAL OR REMOVAL OF A PARTICIPANT FROM THE PROTOCOL 6
15.4.6 COMPLIANCE WITH THE PROTOCOL, MONITORING, AND FDA INSPECTIONS 6
15.4.7. INFORMED CONSENT OF RESEARCH SUBJECTS 8
15.4.8. RECORDKEEPING REQUIREMENTS AND RETENTION OF TEST ARTICLE SPECIMENS FOR BIOAVAILABILITY/BIOEQUIVALENCE (BA/BE) STUDIES 10
15.4.9 REQUIRED REPORTS 12
15.4.10 INVESTIGATOR REPORTING OF UNANTICIPATED PROBLEMS, INCLUDING ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS 12
15.4.11 ADDITIONAL REPORTING RESPONSIBILITIES OF SPONSOR-INVESTIGATORS: 14
15.4.12 PREMATURE TERMINATION OR SUSPENSION OF A TRIAL 14
15.5 RESPONSIBILITIES OF THE IRB WHEN REVIEWING RESEARCH INVOLVING INDS AND/OR IDES 16
15.5.1 REVIEW OF IND/IDE STATUS 16
15.5.2 GENERAL CONSIDERATIONS FOR IRB REVIEW OF RESEARCH INVOLVING INDS OR IDES 16
15.5.3 FDA INSPECTIONS AND AUDITS OF NIH IRBS 17

DHHS/NIH/OD/OIR/OHSRP

15.6 POLICY RELATED TO EMERGENCY USE AND EXPANDED ACCESS TO INVESTIGATIONAL DRUGS AND DEVICES 17

15.7 RESPONSIBILITIES OF THE OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS (OHSRP) 17

LIST OF APPENDICES 19

APPENDIX A - DEFINITIONS 20

APPENDIX B: LINKS TO WEBSITES 27

SOP 15 RESEARCH REGULATED BY THE FOOD AND DRUG ADMINISTRATION (FDA): GENERAL PROCEDURES FOR BOTH IND AND IDE APPLICATIONS

15.1 DEFINITIONS AND LINKS TO WEBSITES

Terms that first appear below in **bold** and with an **asterisk** are defined in Appendix A "Definitions". Links to websites are provided in Appendix B "Links to Websites".

15.2 PURPOSE

This policy describes general procedures to be followed by NIH investigators, NIH IRBs, NIH institutional officials and others as appropriate when FDA-regulated research involving human **drugs*** (including **biological products***) or medical devices is conducted at the NIH. Where noted, this policy also describes some of the requirements under applicable laws and FDA regulations. For a more comprehensive listing of FDA's requirements for the conduct of human drug and device studies, refer to 21 CFR parts 11, 50, 54, 56, 312, and 812.

15.3 POLICY

NIH researchers will conduct research that involves test articles* and human subjects* (i.e., clinical investigations*, in accordance with relevant FDA and Department of Health and Human Services (DHHS) regulatory requirements and consistent with the Guideline for Good Clinical Practice* (GCP) as adapted by the FDA (Appendix B "Links to Websites"). Additional procedures specific to FDA-regulated IND* and IDE* research are detailed under SOP 15A "Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)" and SOP 15B "Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications." In their review of this research, NIH IRBs will comply with the applicable requirements set forth in FDA regulations, 21 CFR part 56 (Appendix B "Links to Websites") and those of DHHS, 45 CFR 46 (Appendix B "Links to Websites"). For a comparison between the FDA and DHHS regulations, see Appendix B "Links to Websites".

DHHS/NIH/OD/OIR/OHSRP

15.4 RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR (PI)

The responsibilities listed here relate specifically to FDA-regulated drug and device research conducted by NIH investigators and are in addition to those provided in SOP 19 "Investigator Responsibilities".

15.4.1 GENERAL RESPONSIBILITIES AND COMMUNICATION WITH THE IRB

A. General responsibilities: **Investigators*** will carry out clinical investigation of drugs or medical devices in accordance with FDA regulations (21 CFR parts 312 and 812) and guidelines (see FDA Guidance Documents and Information Sheets regarding good clinical practice and the conduct of clinical trials (Appendix B "Links to Websites"). Principal Investigators (PIs) will also adhere to specific IRB requirements, NIH Standard Operating Procedures (SOPs) and any NIH Institute-specific procedures or requirements.

   1. The term Principal Investigator is defined in SOP 19 "Investigator Responsibilities". A PI will also be an "investigator" under FDA regulations. Therefore, in this SOP the terms are used interchangeably.

B. Prospective IRB review and approval:

   1. Before research begins, the PI will obtain IRB approval of the protocol, any consent document(s), and any other information to be provided to subjects, consistent with SOP 7 "Requirements for the Ethical and Regulatory Review of Research by NIH Institutional Review Boards."

   2. At initial submission, the PI will complete the NIH Intramural Clinical Protocol Application form and, if the research involves investigational drugs or devices, inform the IRB whether the research requires an IND (see SOP 15A "Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products) or IDE (see SOP 15B "Research Regulated by the Food and Drug Administration (FDA): Information and Policies for IDE Applications"). If the research involves investigational drugs or devices, or the use of commercially available products for an off-label use and there is no IND in effect or no approved IDE, the PI must provide the IRB with a rationale why such an application is not required. If an IND or IDE is required, in addition to the IND/IDE number, the PI will

DHHS/NIH/OD/OIR/OHSRP

provide the IRB with written communication from the FDA that it is safe to proceed with the study.

3. **Investigator's Brochure***: The PI will provide any extant Investigator's Brochure in the submission of the protocol to the IRB. If the Investigator's Brochure is updated during the trial, the PI will provide the updated version to the IRB.

4. Amendments to previously approved research: The PI will obtain prospective IRB review and approval of proposed amendments to previously approved research consistent with SOP 10 "Amendments to IRB-approved Research."

5. Continuing review: The PI is responsible for submitting continuing reviews of research protocols consistent with SOP 9 "Continuing Review by the Convened IRB."

C. Reporting unanticipated problems, including **adverse events*** and **unanticipated adverse device effects*** to the IRB: The PI will promptly report to the IRB any unanticipated problems involving risks to subjects and others and any unanticipated adverse device effects (see FDA regulations 21 CFR 312.66 and 21 CFR 812.150(a)(1)), and SOP 16 "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations."

D. Responsibilities of a PI who is also a **Sponsor-Investigator***: A sponsor-investigator is defined as 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." When the PI is also the sponsor-investigator, the PI is responsible for assuring the IRB that s/he has reviewed the "Information for Sponsor-Investigators Submitting Investigational New Drug Applications" (Appendix B "Links to Websites") or information regarding the "IDE Approval Process" (Appendix B "Links to Websites") and will comply with the regulatory responsibilities of a sponsor and an investigator.

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/IDE, maintaining an effective IND/IDE with respect to the

DHHS/NIH/OD/OIR/OHSRP

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 in 21 CFR 312 Subpart D and 21 CFR 812 Subpart C.

E. Research records: See 15.4.8, below.

F. QI/QA monitoring of and compliance with the protocol (see Section 15.4.6 below).

15.4.2. INVESTIGATOR QUALIFICATIONS AND SUPERVISORY RESPONSIBILITIES

A. Qualifications:

1. 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 an up-to-date *curriculum vitae* and/or other relevant documentation when requested by the sponsor, the IRB and/or the regulatory authority(ies).

2. The PI and other investigators, as appropriate, should be thoroughly familiar with the appropriate use of the investigational product(s) described in the protocol, in the current Investigator's Brochure, and in other information sources provided by the sponsor.

3. All investigators should be aware of, and conduct the research consistent with, the Guideline for Good Clinical Practice (GCP). (Appendix B “Links to Websites”.)

B. Supervisory Responsibilities: Investigators may delegate study-related tasks to others. When an investigator delegates tasks, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated and is accountable for violations of FDA regulations resulting from a failure to adequately supervise the conduct of the study. Such delegations will be noted in the regulatory binder. The PI will also meet the NIH criteria set forth in SOP 19 “Investigator Responsibilities”.

15.4.3. ADEQUATE RESOURCES, INCLUDING QUALIFIED STAFF, TO CONDUCT THE RESEARCH

A. The PI should be able to demonstrate to the IRB (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the anticipated recruitment period.

B. The PI should have sufficient time to conduct and complete the trial within the anticipated trial period.

C. The PI should have available an adequate number of qualified staff for the foreseen duration of the trial to conduct the trial properly and safely.

D. The PI should maintain a list of appropriately qualified persons to whom s/he has delegated significant trial-related activities.

E. The PI will ensure that there are adequate financial resources, facilities and space in which to conduct the research.

15.4.4. MEDICAL CARE OF RESEARCH SUBJECTS

Under FDA regulations, investigators are responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial (21 CFR 312.60 and 812.100). Consistent with this requirement, it is NIH policy that:

A. Medical decision making: A qualified physician (or dentist, when appropriate), who is an investigator will be responsible for all trial-related medical decisions.

B. Ensuring adequate medical care (see Appendix B “Links to Websites”): During and following a subject's participation in a trial, the PI will ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The PI, or other appropriately designated person should inform a subject when medical care is needed for conditions or illnesses unrelated to the study intervention or the disease or condition under study when such condition or illness is readily apparent or identified through the screening procedures and eligibility criteria for the study.

C. Communication with the subject’s primary physician: It is recommended that the PI put into place procedures to inform the subject's primary physician

DHHS/NIH/OD/OIR/OHSRP

about the subject's participation in the trial (if the subject has a primary physician and he/she agrees to the primary physician being informed).

15.4.5. WITHDRAWAL OR REMOVAL OF A PARTICIPANT FROM THE PROTOCOL

A. A subject can leave the study with or without reason at any time. Although s/he is not obliged to give the reason(s) for withdrawing prematurely from a study, the PI should make a reasonable effort to ascertain the reason(s), while respecting the subject's rights.

B. The investigator may remove the subject from participation if s/he is not complying with the requirements of the study, or if the investigator deems that it is not safe for the subject to stay on the study.

C. Withdrawal or removal of a subject should be documented in the medical record.

D. For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot provide that the subject may remove his or her data. For more information about FDA's policy regarding already-accrued data relating to subjects who discontinue participation in research, refer to FDA's guidance for sponsors, clinical investigators, and IRBs entitled "Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials" (see Appendix B "Links to Websites")

15.4.6 COMPLIANCE WITH THE PROTOCOL, MONITORING, AND FDA INSPECTIONS

A. Compliance with the sponsor- and IRB-approved protocol:

1. Under FDA regulations, the investigator is responsible for ensuring that the study is conducted according to the investigational plan, including the protocol.

2. Deviations from previously approved research:

   a. Neither the PI nor other researchers nor research staff will deviate from the protocol without agreement by the sponsor and prospective review

DHHS/NIH/OD/OIR/OHSRP

and documented approval by the IRB except where necessary to eliminate an immediate hazard(s) to trial subjects.

b. Deviations from previously-approved research made to avert immediate harm to subjects will be reported to the NIH IRB and the sponsor as specified in SOP 16 “Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations” (see SOP 16 for the NIH Problem Report Form), and in accordance with FDA regulations. See 21 CFR 312.66 and 812.150(a)(4).

c. Changes in minor administrative or logistical aspects of the protocol (e.g., change in monitor, changes in telephone numbers) do not need prospective approval of the sponsor but require IRB review and approval (see SOP 7A “Requirements for Expedited Review of Research by NIH Institutional Review Boards.”)

d. Randomized Procedures and Unblinding: The PI will follow the trial's randomization procedures, if any, and ensure that the code is broken only in accordance with the protocol. If the trial is blinded the PI will promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding or unblinding due to a serious adverse event).

B. Monitoring of clinical investigations:

1. Under FDA regulations (21 CFR 812.40 and 312.50, see Appendix B “Links to Websites”), the sponsor is required to ensure proper monitoring of the study. Sponsors are also required to select monitors qualified by training and experience (21 CFR 312.53(d) and 812.43(d)). To avoid any conflict of interest, it is NIH policy that an NIH PI sponsor-investigator should assign an independent, NIH IRB-approved monitor for the study.

2. The PI and other investigators, as appropriate, agree to cooperate with monitoring and auditing by the sponsor and NIH IC QI/QA programs (see SOP 23 “Quality Management System for the NIH HRPP.”)

C. FDA inspections: Investigators and IRBs must make records available for FDA inspection in accordance with 21 CFR 56.115(b), 312.68 and 812.145. NIH researchers and IRBs (see Section 15.5.3) who are informed of an FDA inspection or audit should immediately notify their Clinical Director(s) and the Director, OHSRP.

DHHS/NIH/OD/OIR/OHSRP

1. Researchers must cooperate with guidance provided by the Clinical Director and OHSRP staff with respect to such audit(s) or inspection(s), including allowing appropriate NIH personnel to participate in the inspection or audit.

2. Any written responses to the FDA submitted by NIH researchers must first be approved by the Clinical Director and the Director, OHSRP. The researcher must provide a draft response to the Clinical Director and OHSRP Director at least two days before it must be submitted to the FDA.

    a. If there is disagreement between a researcher and a Clinical Director or the OHSRP Director about a response to the FDA, the Deputy Director for Intramural Research (DDIR) will make a decision about the appropriate response.

15.4.7. INFORMED CONSENT OF RESEARCH SUBJECTS

A. General considerations: The PI will ensure that informed consent is obtained and documented as required by the NIH IRB-approved protocol. The PI will comply with the applicable regulatory requirement(s) (including FDA regulations (see Appendix B "Links to Websites") and will follow NIH SOP 12 "Requirements for Informed Consent from Research Subjects" and GCP section 4.8 (Appendix B "Links to Websites").

B. Informed Consent Document: In addition to satisfying FDA requirements and the requirements in SOP 12, the consent document for applicable FDA-regulated clinical trials must include the following statement: "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." (21 CFR 50.25(c))

C. **Non-therapeutic research***: FDA-regulated research may include non-therapeutic trials (trials in which there is no anticipated direct clinical benefit to the subject). Such research may be conducted at the NIH in the following circumstances:

1. With the written informed consent of the subject, or

DHHS/NIH/OD/OIR/OHSRP

2. With the written informed consent of a legally authorized representative provided the following conditions are fulfilled:

    a. The objectives of the trial cannot be met by means of a trial involving subjects who can give their own informed consent.

    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 of the IRB is expressly sought on the inclusion of such subjects, and the IRB's written approval covers this aspect. In the NIH IRB review of this research, the PI and IRB will follow the requirements of SOP 14A "Research involving Vulnerable Subjects - General Considerations."

D. Informed consent requirements for emergency research:

1. General considerations: An NIH PI may conduct research under the requirements of 21 CFR 50.24 (see Appendix B "Links to Websites"), provided it is also consistent with the requirements of 45 CFR 46.

2. For more information regarding emergency use of investigational drugs see SOP 15A "Research Regulated by the Food and Drug Administration (FDA) and for devices see SOP 15B.

E. Waiver of requirement to document the consent process:

2. Unless criteria for an exception from the general requirements for consent (21 CFR 50.23) or an exception for emergency research are met (21 CFR 50.24), no investigator may involve a human being as a subject in research covered by the FDA regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Unless there is an exception (21 CFR 56.109(c)), informed consent shall be documented by the use of a written

DHHS/NIH/OD/OIR/OHSRP

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.

3. The IRB may waive the requirement to have a subject or subject's legally authorized representative sign a written consent form in certain circumstances or waive the requirement to obtain consent by determining that the regulatory criteria for waivers are met (see 21 CFR 56.109(c) for more details).

4. In cases where the IRB waives the requirement to obtain signed consent forms from subjects, the IRB may require the investigator to provide subjects with a written statement regarding the research (see 21 CFR 56.109(d)).

F. Informed Consent for In Vitro Diagnostic Devices Using Leftover Human Specimens that are not Individually Identifiable

When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects. However, in its guidance for sponsors, IRB's, investigators and FDA staff, issued April, 2006 (*Guidance on Informed Consent for In Vitro Diagnostic Devices Using Leftover Human Specimens that are not Individually Identifiable)*, FDA indicated the following: "FDA does not intend to object to the use, without informed consent, of leftover human specimens -- remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded -- in investigations that meet the criteria for exemption from the Investigational Device Exemptions (IDE) regulation at 21 CFR 812.2(c)(3), as long as subject privacy is protected by using only specimens that are not individually identifiable. FDA also intends to include in this policy specimens obtained from specimen repositories and specimens that are leftover from specimens previously collected for other unrelated research, as long as these specimens are not individually identifiable."

15.4.8. RECORDKEEPING REQUIREMENTS AND RETENTION OF TEST ARTICLE SPECIMENS FOR BIOAVAILABILITY/BIOEQUIVALENCE (BA/BE) STUDIES

A. **Accuracy of Records**: Investigators' recordkeeping requirements under FDA regulations are described at 21 CFR 312.62 and 812.140. Consistent with these requirements, it is NIH policy that the PI must prepare adequate and

DHHS/NIH/OD/OIR/OHSRP

accurate case histories, records of subjects' conditions before, during and after the clinical investigation, progress notes that record observations and other data about each subject and assure that research data is verifiable in the source documents. These records must be made available for inspection as needed and in accordance with FDA regulations at 21 CFR 312.68 and 812.145.

B. **Case Report Form*** (CRF): Consistent with FDA requirements, it is NIH policy that:

1. The PI will ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRF and in all required reports.

2. Any 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 both to written and electronic changes or corrections.

    a. Sponsors should provide guidance to PIs and/or PIs' designated representatives on making such corrections.

    b. Sponsors should have written procedures to assure that corrections in CR data made by sponsors' designated representatives are documented, as necessary, and are endorsed by the PI.

    c. The PI will retain records of all corrections.

C. **Regulatory Binder**: Retention of trial documents: Investigators must maintain the trial records as required by the applicable regulatory requirement(s), including FDA regulations (see 21 CFR 312.62(c) and 812.140(d)). It is NIH policy that the PI should also maintain trial documents consistent with *Essential Documents for the Conduct of a Clinical Trial* (Appendix B "Links to Websites"). This is commonly referred to as a "regulatory binder."

D. **Record Retention**: At the closure of the trial, the PI will retain the records and reports required for the ***longest*** of the following intervals: 1) at least 3 years as required by the MAS policy M93-1, "Research Involving Human Subjects at the Clinical Center: Structure and Process" (see Appendix B "Links to Websites") two years after a marketing application is approved for the drug or, 3) if an application is not approved for the drug, records must be maintained

DHHS/NIH/OD/OIR/OHSRP

for 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been notified (21 CFR 312.57(c)). For more information see SOP 11A "Closure of an IRB-approved Protocol."

E. **Reserve Testing Samples for BA/BE Studies**: The PI shall retain reserve samples of any test article and reference standard identified in, and used in any relevant bioequivalence or bioavailability studies and release the reserve samples to FDA upon request, (21 CFR 312.57 (d), 21 CFR 320.38, 21 CFR 320.63). At the Clinical Center, the Pharmaceutical Development Service retains samples of the test article. For more information see SOP 11A "Closure of an IRB-approved Protocol"

F. **Record of financial agreements**: The financial aspects of the trial should be documented in an agreement between the sponsor and the PI and NIH.

15.4.9 REQUIRED REPORTS

A. Required reports for IND and IDE research are detailed in SOPs 15A "Research Regulated by the Food and Drug Administration (FDA). Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products)" and 15B "Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications".

B. Other progress reports: Consistent with GCP, NIH PIs will provide other written reports, as required by the IRB-approved protocol, to the sponsor, the IRB, and, when required, to the FDA on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects. (Appendix B "Links to Websites", Guideline for Good Clinical Practice)

C. Final Report(s) and Submission of Data by the PI. Upon completion or termination of the trial, the PI will provide the sponsor with all required reports and data, the IRB with a summary of the trial's outcome, and provide any final reports to the sponsor and/or the FDA required by applicable laws and regulations.

15.4.10 INVESTIGATOR REPORTING OF UNANTICIPATED PROBLEMS, INCLUDING ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

DHHS/NIH/OD/OIR/OHSRP

A. Under FDA regulations, investigators are required to report promptly serious adverse events and unanticipated adverse device effects to sponsors (see 21 CFR 312.64(b) and 812.150(a) (1)). Specific requirements and timeframes for reporting differ for drug and device studies. For more information about the FDA's requirements and policies regarding reporting of adverse events and unanticipated adverse device effects for drug and device clinical investigations, refer to FDA's regulations at 21 CFR parts 312 and 812 and guidance for sponsors, clinical investigators, and IRBs entitled "Adverse Event Reporting to IRBs - Improving Human Subject Protection."

B. Additional regulations require that unanticipated problems be reported to the IRB. These additional reporting requirements pertain to FDA-regulated research (See SOP 16 "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations").

C. It is NIH policy that:

1. Investigators should immediately report all **serious adverse events*** (SAEs) and/or **unanticipated adverse device effects*** to the sponsor and to the IRB if they are also unanticipated problems. Reporting will be consistent NIH HRPP requirements in SOP 16 "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations." 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.

2. Adverse events, unanticipated adverse device effects, and/or laboratory abnormalities identified in the protocol as critical to safety evaluations must be reported to the sponsor according to regulatory reporting requirements and within the time periods specified by the sponsor in the protocol.

3. For deaths that are reportable under the IRB-approved protocol, the investigator will supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

4. Investigators will report all other events to the Clinical Director and/or IRB as outlined in SOP 16 "Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations".

DHHS/NIH/OD/OIR/OHSRP

15.4.11 ADDITIONAL REPORTING RESPONSIBILITIES OF SPONSOR-INVESTIGATORS:

A. Under FDA regulations, sponsor-investigators are required to report promptly serious adverse events and unanticipated adverse device effects to the FDA (see 21 CFR 312.64(b) and 812.150(a) (1)). Specific requirements and timeframes for reporting differ for drug and device studies. For more information about the FDA's requirements and policies regarding reporting of adverse events and unanticipated adverse device effects for drug and device clinical investigations, refer to FDA's regulations at 21 CFR parts 312 and 812.

15.4.12 PREMATURE TERMINATION OR SUSPENSION OF A TRIAL

A. By the PI: If the PI terminates, or suspends a trial without prior agreement of the sponsor, the PI will inform the IRB and the sponsor. Communication from the PI to the IRB and the sponsor will include a detailed written explanation of the termination or suspension.

B. By the sponsor: If the sponsor terminates or suspends a trial, the PI should promptly inform the IRB and provide it with a detailed written explanation of the termination or suspension.

C. By an IRB: If an NIH IRB terminates or suspends its approval of a trial the PI will inform the sponsor. The IRB will report its actions to the investigator, NIH Institutional officials, and FDA consistent with SOP 24 "NIH Reporting to the OHRP and the FDA Regarding Unanticipated Problems, Serious or Continuing Non-Compliance or Terminations and Suspensions" and in accordance with FDA regulations (21 CFR 56.113).

D. Informing research participants about suspension/termination: If the trial is terminated prematurely or suspended for any reason, the PI will promptly inform the trial subjects, and should assure appropriate therapy and follow-up for the subjects, according to procedures in SOP 11 "Suspensions and Terminations of IRB-approved Research and Administrative Holds."

E. Informing regulatory authority(ies): Where required by the applicable regulatory requirement(s), the PI must inform the regulatory authority(ies).

15.4.13 SUBJECT WITHDRAWAL FROM AN FDA REGULATED STUDY

DHHS/NIH/OD/OIR/OHSRP

A. The FDA has provided guidance regarding the policy on the withdrawal of subjects from a clinical investigation, whether the subject elects to discontinue further interventions or the clinical investigator terminates the subject's participation in further interventions. See Appendix B-Links to Websites for FDA's *Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials.*

1. According to FDA regulations, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

2. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

3. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

4. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

DHHS/NIH/OD/OIR/OHSRP

B. Although withdrawal of a subject from a clinical investigation is not the same as closure of a protocol, the transition steps discussed in SOP 11A may be appropriate to consider for subjects who is withdraw from a study.

15.5 RESPONSIBILITIES OF THE IRB WHEN REVIEWING RESEARCH INVOLVING INDS AND/OR IDES

15.5.1 REVIEW OF IND/IDE STATUS

The IRB administrative staff, in collaboration with the IRB Chair, will review the documents provided by the PI (see SOP 15A "Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products") and SOP 15B "Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications.") and confirm whether the research requires an IND/IDE and that there is appropriate supporting documentation.

15.5.2 GENERAL CONSIDERATIONS FOR IRB REVIEW OF RESEARCH INVOLVING INDS OR IDES

A. The IRB will review the research protocol in accordance with applicable DHHS regulations (see SOP 8 "Procedures and Required Documentation for Initial Review of Protocols by a Convened NIH Institutional Review Board."), and FDA regulations (see 21 CFR part 56, Appendix B "Links to Websites", for FDA regulations related to IRBs).

B. If the IRB does not have the necessary expertise to review the specific research activity (see 21 CFR 56.107 for FDA requirements related to IRB membership), additional consultation will be sought consistent with SOP 2 "IRB Membership and Structure".

C. The IRB will review proposed advertising to ensure that advertisements do none of the following:

   1. Make claims, 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;

DHHS/NIH/OD/OIR/OHSRP

2. Use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational;

3. Allow “compensation" for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

D. Additional responsibilities and procedures for IRB review of INDs are detailed in SOP 15A “Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products”) and for review of IDEs in SOP 15B “Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications.”

15.5.3 FDA INSPECTIONS AND AUDITS OF NIH IRBS

A. IRBs must make records available for FDA inspection in accordance with 21 CFR 56.115(b), and 812.145. NIH IRBs that are informed of an FDA inspection or audit should immediately notify their Clinical Director(s) and the Director, OHSRP.

1. Any written responses by an NIH IRB Chair to the FDA must be submitted for approval to the Clinical Director and the Director, OHSRP at least two days before the Chair’s submission to the FDA.

15.6 POLICY RELATED TO EMERGENCY USE AND EXPANDED ACCESS TO INVESTIGATIONAL DRUGS AND DEVICES

See SOP 15A “Research Regulated by the Food and Drug Administration (FDA): Information and Policies Specific to Research Involving Investigational New Drugs (Including Biological Products”) and SOP 15B “Research Regulated by the Food and Drug Administration (FDA): Information and Policies for Investigational Device Exemption (IDE) Applications.”

15.7 RESPONSIBILITIES OF THE OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS (OHSRP)

A. The OHSRP, in collaboration with the Institutes, will provide required education and training programs for investigators holding an IND or IDE. See SOP 25 "Training Requirements for the NIH HRPP."

B. The OHSRP will be informed by PIs and/or NIH IRBs of any FDA audits/inspections as discussed in 15.4.6.C.

C. OHSRP will report unanticipated problems, serious or continuing noncompliance or terminations or suspensions to the FDA in accordance with SOP 24 "NIH Reporting to OHRP and the FDA Regarding Unanticipated Problems, Serious or Continuing Non-Compliance or Terminations or Suspensions" as follows:

   1. For Drug Products, to the Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research.

   2. For Biologic Products, to the Bioresearch Monitoring Branch, Division of Inspections and Surveillance, Office of Compliance and Biologics Quality.

   3. For Medical Devices, to the Center for Devices and Radiological Health.

DHHS/NIH/OD/OIR/OHSRP

LIST OF APPENDICES

Appendix A: Definitions

Appendix B: Links to Websites

APPENDIX A - DEFINITIONS

Except where noted otherwise, the definitions listed below are for the purpose of this SOP and are not necessarily found in the Federal Food, Drug, and Cosmetic Act (FDCA), the Public Health Service Act, FDA regulations, or other applicable laws and regulations.

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

B. **Biological products** - see definition of “Test Article”.

C. **Case Report Form (CRF)**, is a protocol-specific form designed by the Principal Investigator or sponsor to enable the sponsor to collect data from each participating site and on each patient participating in a clinical trial.

D. **Clinical investigation**: FDA regulations define a clinical investigation as any experiment that involves a test article (e.g., drug or medical device – see definitions of “investigational drug” and “investigational device”) and one or more human subjects (see definition of “human subjects”) that is subject to requirements for prior submission to the FDA or is intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit, (See Appendix B “Links to Websites” for the links to definitions under 21 CFR 50.3(c)) and 21 CFR 56.102(c)). The terms research, clinical research, clinical study, study and clinical investigation are synonymous for the purposes of this SOP.

   For drugs, a clinical investigation is “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects . . . an experiment is any use of the a drug except for the use of a marketed [approved] drug in the course of medical practice.” 21 CFR 312.3(b).

E. **Color Additive**:21 CFR 70.3 (f): Any material, not exempted under section 201(t) of the act, that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source and that, when added or applied to a food, drug, or cosmetic or to the human body or any part thereof, is capable (alone or through reaction with another substance) of imparting a color thereto. Substances capable of imparting a color to a container for foods, drugs, or cosmetics are not color additives unless

DHHS/NIH/OD/OIR/OHSRP

the customary or reasonably foreseeable handling or use of the container may reasonably be expected to result in the transmittal of the color to the contents of the package or any part thereof. Food ingredients such as cherries, green or red peppers, chocolate, and orange juice which contribute their own natural color when mixed with other foods are not regarded as color additives ; but where a food substance such as beet juice is deliberately used as a color, as in pink lemonade, it is a color additive. Food ingredients as authorized by a definitions and standard of identity prescribed by regulations pursuant to section 401 of the act are color additives, where the ingredients are specifically designated in the definitions and standards of identity as permitted for use for coloring purposes. An ingredient of an animal feed whose intended function is to impart, through the biological processes of the animal, a color to the meat, milk, or eggs of the animal is a color additive and is not exempt from the requirements of the statute. This definition shall apply whether or not such ingredient has nutritive or other functions in addition to the property of imparting color. An ingested drug the intended function of which is to impart color to the human body is a color additive. For the purposes of this part, the term color includes black, white, and intermediate grays, but substances including migrants from packaging materials which do not contribute any color apparent to the naked eye are not color additives (See Appendix B “Links to Websites”.)

F. **Drug**:

1. A substance recognized by an official pharmacopoeia or formulary

2. A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease

3. A substance (other than food) intended to affect the structure or any function of the body

4. A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device

5. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

G. **Emergency use**: FDA regulations define emergency use as “the use of a test article on a human subject in a life-threatening situation in which no standard

DHHS/NIH/OD/OIR/OHSRP

acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval", 21 CFR 56.102(d).

H. **Food Additives**: 21 CFR 170.3 (e)(1): Food additives include all substances not exempted by section 201(s) of the act, the intended use of which results or may reasonably be expected to result, directly or indirectly, either in their becoming a component of food or otherwise affecting the characteristics of food. A material used in the production of containers and packages is subject to the definition if it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food packed in the container. "Affecting the characteristics of food" does not include such physical effects, as protecting contents of packages, preserving shape, and preventing moisture loss. If there is no migration of a packaging component from the package to the food, it does not become a component of the food and thus is not a food additive. A substance that does not become a component of food, but that is used, for example, in preparing an ingredient of the food to give a different flavor, texture, or other characteristic in the food, may be a food additive (see Appendix B "Links to Websites".)

I. **The Guideline for Good Clinical Practice (GCP)**: GCP is an international ethical and scientific standard developed by the International Conference on Harmonisation (ICH) for designing, conducting, recording and reporting trials involving the participation of human subjects consistent with the principles of the Declaration of Helsinki. FDA published this guidance in the Federal Register on May 9, 1997 (62 FR 25692) (see Appendix B "Links to Websites".)

J. **Human subject**: FDA regulations define a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article [see definition of "test article"] or as a control. A subject may be either a healthy human or a patient", see 21 CFR 50.3(g) and 21 CFR 56.102(e).

For drugs, a subject "means a human who participates in an investigation, either as a recipient of the investigational new drug [see definition of investigational drug] or as a control. A subject may be a healthy human or a patient with a disease." 21 CFR 312.3(b).

For medical devices, a subject "means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device [see definition of "investigational device] is used or as a control. A subject may be in normal health or may have a medical condition or disease." 21 CFR 812.3(p).

DHHS/NIH/OD/OIR/OHSRP

K. **Humanitarian Use Device (HUD)**; A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year, 21 CFR 814.3(n).

L. **Investigational device**: "means a device, including a transitional device that is the object of an investigation", 21 CFR 812.3(g).

M. **IDE**: An IDE means an application for an Investigational Device Exemption in accordance with 21 CFR part 812.

N. **Investigational 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" 21 CFR 312.3(b).

O. **IND**: An IND means an Investigational New Drug application in accordance with 21 CFR Part 312.

P. **Investigator**: "[A]n individual who conducts a clinical investigation, i.e., under whose immediate direction the test article [see definition of "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", 21 CFR 50.3(d).**

Q. **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) on human subjects." The Guideline for Good Clinical Practice at section 6 (see Appendix B "Links to Websites".)

R. **Non-Significant Risk (NSR) Device**: An investigational device that does not meet the definition of a significant risk device (see definition of "significant risk device, below).

S. **Non-Therapeutic Trial**: In the Guideline for Good Clinical Practice, FDA describes this as a trial in which there is no anticipated direct clinical benefit to the subject (see GCP at sections 4.8.13 and 4.8.14 in Appendix B "Links to Websites".)

T. **Serious adverse event**: An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator or sponsor, it results in any

DHHS/NIH/OD/OIR/OHSRP

of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity or 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 a serious adverse drug experience when, based upon 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.

U. Significant Risk (SR) Device is defined in FDA regulations as 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; or

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; or

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.

See 21 CFR 812.3(m).

V. Sponsor: A person (or other entity) "who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article [see definition of "test article"] is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A[n] [entity] other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct a clinical investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators." 21 CFR 50.3(e); see also 21 CFR 56.102(j).

W. Sponsor-investigator: An "individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction

DHHS/NIH/OD/OIR/OHSRP

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" (see 21 CFR 312.3 and 21 CFR parts 50.3(f) and 56.102(k).)

X. **Suspected adverse reaction** (21 CRF 312.32(a)) means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Y. **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 [FDCA] or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n)." See Appendix B "Links to Websites", 21 CFR 50.3(j); see also 21 CFR 56.102(l). The definitions of the various examples of test articles are as follows:

1. Medical devices: A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is-- (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes" Section 201(h) of the FDCA (see Appendix B "Links to Websites".)

2. Biological products: Under the Public Health Service Act (42 USC 262(i)), the term "biological product" "means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings" (see Appendix B "Links to Websites".)

Z. **Unanticipated Adverse Device Effect**: An unanticipated adverse device effect is any serious adverse effect on health or safety, 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 application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. See FDA regulation at 812.150(a)(1)

APPENDIX B: LINKS TO WEBSITES

A. FDA Form 1572:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

B. Guideline for Good Clinical Practice (GCP):http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

C. Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs):
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm

D. IDE Approval
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm

E. Ensuring adequate medical care:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

F. FDA requirements for data retention when subjects withdraw from FDA-regulated clinical trials:
http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf

G. Essential Documents For The Conduct Of A Clinical Trial: See Section 8 of the following link:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

H. FDA regulations -- IND annual reports (21 CFR 312.33):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.33

I. FDA regulations -- IND safety reports (21 CFR 312.32):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=312.32

DHHS/NIH/OD/OIR/OHSRP

J. FDA IDE regulations (21 CFR part 812):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812

K. FDA IND regulations 21 CFR part 312 (exemptions from these regulations provided at 312.2):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

L. FDA IDE regulations, "Abbreviated Requirements" (21 CFR 812.2(b)):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=812.2

M. FDA regulations -- Exception from general requirements for informed consent (21 CFR 50.23):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.23

N. FDA regulations -- Exemptions from IRB requirement (21 CFR 56.104):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.104

O. FDA regulations -- Exception from informed consent for emergency research (21 CFR 50.24):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24

P. FDA regulations -- Expanded Access to investigational Drugs for Treatment Use (21 CFR 312.300-312.320):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.9

Q. FDA emergency device use:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm#compassionateuse

R. FDA regulations 21 CFR 814, Premarket Approval of Medical Devices (Subpart H – Humanitarian Use Devices)
S. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1

DHHS/NIH/OD/OIR/OHSRP

T. FDA regulations -- Institutional Review Boards (21 CFR part 56):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56

U. FDA Regulations -- "Protection of Human Subjects" (21 CFR part 50):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=5

V. FDA Device Advice:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

W. Comparison of FDA's regulations at 21 CFR parts 50 and 56 and HHS Human Subject Protection Regulations:
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm

X. HHS Human Subject Protection Regulations 45 CFR 46:
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

Y. Color Additive: 21 CFR 170.3 (e)(1):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=70.3&SearchTerm=color%20additive

Z. Food Additives: 21 CFR 170.3 (e)(1):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=170.3&SearchTerm=170%2E3

AA. Medical devices:
http://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm#_Toc294261435 and
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm

BB. Biological Product, 21 CFR 600.3(h):
http://www.fda.gov/RegulatoryInformation/Legislation/ucm149278.htm

CC. 21 CFR 50.3 Definitions:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.1

DHHS/NIH/OD/OIR/OHSRP

DD. 21 CFR 56.102 Definitions:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=56.102

EE. Test Article, 21 CFR 50.3(j):

a. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.1

FF. MAS Policy M93-1, Research Involving Human Subjects at the Clinical Center: Structure and Process:

a. http://cc-internal.cc.nih.gov/policies/PDF/M93-1.pdf

GG. Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials:
http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126489.pdf