

GEORGIA INSTITUTE OF TECHNOLOGY
Regulatory Affairs and Clinical Trials

Policies & Procedures Manual

December 2022

POLICIES & PROCEDURES

Revisions and Updates

December 2022

- V: Clarified that the Office of Research Integrity Assurance can make IDE Exempt determinations.

November 2022

- Appendix 10: Updated to remove contact information for previous director and revised name of committee to reflect the actual name of the IRB.

July 2022

- I: Updated to reflect the current Georgia Institute of Technology Strategic Plan
- III: Updated information regarding Phase II and Phase II Cancer Clinical Trial subsection to reflect current Georgia code regarding this topic.
- V: Updated formatting
- XIII: Updated to include the OHRP definition of a clinical trial, procedures for posting informed consent documents, and procedures for submitting clinical trial results.
- XIV: Updated links.
- XIX: Updated listed phone numbers and formatting.
- Appendices: Updated to reflect new appendices (Appendix 11 and 12).
- Appendix 2: Fixed typos.
- Appendix 3: Fixed reference to another appendix.
- Appendix 10: Updated to reflect current version of the document.
- Appendix 11: Added this appendix to the document.
- Appendix 12: Added this appendix to the document.
- Glossary: Updated the definition of the term “Clinical Trial” and fixed a reference to an appendix.

**GEORGIA INSTITUTE OF TECHNOLOGY
Regulatory Affairs and Clinical Trials**

Table of Contents

REVISIONS AND UPDATES	2
TABLE OF CONTENTS	3
I. MISSION	9
II. REGULATORY AFFAIRS AND CLINICAL TRIALS OFFICE OPERATIONS	10
III. STATUTORY BASIS OF REGULATORY AFFAIRS AND CLINICAL TRIALS OFFICE AUTHORITY	11
A. DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS).....	11
B. FOOD AND DRUG ADMINISTRATION (FDA).....	11
C. STATE OF GEORGIA	11
1. <i>Prisoner Studies</i>	<i>11</i>
2. <i>Genetic Research</i>	<i>12</i>
3. <i>Consent Age.....</i>	<i>12</i>
4. <i>Controlled Substances.....</i>	<i>12</i>
5. <i>Phase II and III Cancer Clinical Trials.....</i>	<i>12</i>
6. <i>Drug Investigation Laws</i>	<i>13</i>
7. <i>Medical and Other Records Privacy</i>	<i>13</i>
8. <i>STD Reporting</i>	<i>14</i>
D. HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)	14
E. DEPARTMENT OF DEFENSE, INCORPORATED BY ADDENDA TO FEDERALWIDE ASSURANCE	15
IV. FOOD & DRUG ADMINISTRATION (FDA) REGULATED PRODUCTS	17
V. MEDICAL DEVICE RESEARCH	19
A. RESEARCH INVOLVING THE USE OF INVESTIGATIONAL MEDICAL DEVICES	19
B. CHECKLIST FOR STUDIES INVOLVING INVESTIGATIONAL DEVICES:	20
C. DETERMINING THE SAFETY OR EFFECTIVENESS OF A DEVICE.....	21
D. FDA DEVICE CLASSIFICATION	23
1. <i>The Three Device Classes and Related Requirements.....</i>	<i>23</i>
2. <i>How to Determine Classification.....</i>	<i>24</i>
E. DETERMINATION OF SIGNIFICANT AND NONSIGNIFICANT RISK IN MEDICAL DEVICE STUDIES.....	25
1. <i>Two Types of Device Studies</i>	<i>25</i>
2. <i>Implications of Differences in Significant and Nonsignificant Risk Devices</i>	<i>25</i>
F. DEVICE LABEL	29
1. <i>Definitions of Label and Labeling.....</i>	<i>29</i>
2. <i>Device Label for an IDE and Abbreviated IDE</i>	<i>30</i>
3. <i>Device Label for an IVD.....</i>	<i>31</i>
G. CONTROL, HANDLING AND DOCUMENTATION OF DEVICES USED IN INVESTIGATIONS	31
H. CASE REPORT FORMS	31
I. QUALITY SYSTEMS REGULATIONS	32

J. RESPONSIBILITIES OF ALL INVESTIGATORS CONDUCTING RESEARCH SUBJECT TO THE FDA REGULATIONS.....	32
1. <i>Maintaining Records.....</i>	33
2. <i>Inspections.....</i>	34
3. <i>Submitting Reports.....</i>	34
4. <i>Investigational Device Distribution and Tracking.....</i>	35
5. <i>Prohibition of Promotion and Other Practices.....</i>	35
6. <i>Annual Progress Reports and Final Reports.....</i>	35
J. ADDITIONAL RESPONSIBILITIES OF A SPONSOR-INVESTIGATOR.....	36
VI. DRUG RESEARCH.....	37
VII. BIOLOGICS RESEARCH.....	40
VIII. COMBINATION PRODUCTS RESEARCH.....	41
IX. INSTITUTIONAL REVIEW BOARD REQUIREMENTS.....	43
A. GENERAL PROVISIONS.....	43
1. <i>Circumstances in Which IRB Review is Required.....</i>	43
2. <i>Exemptions from IRB Requirement.....</i>	44
3. <i>Waiver of IRB Requirement.....</i>	44
B. ORGANIZATION AND PERSONNEL.....	44
C. IRB FUNCTIONS AND OPERATIONS.....	45
1. <i>IRB Review of Research.....</i>	46
2. <i>Expedited Review for Certain Kinds of Research.....</i>	47
3. <i>Criteria for IRB Approval of Research.....</i>	48
4. <i>Review by Institution.....</i>	49
5. <i>Suspension or Termination of IRB Approval of Research.....</i>	49
6. <i>Cooperative Research.....</i>	50
D. RECORDS AND REPORTS.....	50
X. INFORMED CONSENT REQUIREMENTS.....	52
A. GENERAL REQUIREMENTS FOR INFORMED CONSENT.....	52
B. EXCEPTION FROM GENERAL REQUIREMENTS.....	52
C. EXCEPTION FROM INFORMED CONSENT REQUIREMENTS FOR EMERGENCY RESEARCH.....	58
D. ELEMENTS OF INFORMED CONSENT.....	61
E. DOCUMENTATION OF INFORMED CONSENT.....	63
XI. INCLUSION OF MINORS IN CLINICAL RESEARCH.....	65
A. CLINICAL INVESTIGATIONS NOT INVOLVING GREATER THAN MINIMAL RISK.....	65
B. CLINICAL INVESTIGATIONS INVOLVING GREATER THAN MINIMAL RISK BUT PRESENTING THE PROSPECT OF DIRECT BENEFIT TO INDIVIDUAL SUBJECTS.....	65
C. 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.....	66
D. CLINICAL INVESTIGATIONS NOT OTHERWISE APPROVABLE THAT PRESENT AN OPPORTUNITY TO UNDERSTAND, PREVENT, OR ALLEVIATE A SERIOUS PROBLEM AFFECTING THE HEALTH OR WELFARE OF CHILDREN.....	66
E. REQUIREMENTS FOR PERMISSION BY PARENTS OR GUARDIANS AND FOR ASSENT BY CHILDREN.....	67

F. WARDS.....	68
XII. REQUIRED TRAINING	70
A. NIH GCP TRAINING REQUIREMENT	70
1. Purpose	70
B. ADDITIONAL TRAINING REQUIREMENTS.....	71
1. IRB and IACUC Required Training	71
2. DOD Required Training	71
3. Training Requirement for Off-Campus Researchers	71
4. Expired Training.....	71
XIII. CLINICAL TRIALS.....	72
A. DEFINITIONS OF A CLINICAL TRIAL.....	72
1. FDA Definition of an “Applicable Clinical Trial” (ACT).....	72
2. NIH Definition of a Clinical Trial.....	73
3. OHRP Final Rule Definition of a Clinical Trial	73
B. PROCESS FOR REGISTERING CLINICAL TRIALS ON CLINICALTRIALS.GOV	73
C. MAINTENANCE OF CLINICAL TRIALS.....	75
D. SUBMITTING CONSENT FORMS.....	75
E. SUBMITTING CLINICAL TRIAL RESULTS	75
XIV. HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA) FOR PROTECTED HEALTH INFORMATION.....	77
A. DEFINITIONS	77
B. WHAT RESEARCH IS SUBJECT TO THE HIPAA REGULATIONS?	79
C. TYPES OF HEALTH INFORMATION	79
1. Individually Identifiable Health Information (IIHI)	79
2. De-Identified Data Sets	79
3. Limited Data Sets	80
D. AUTHORIZATION (CONSENT) REQUIREMENTS.....	81
1. Elements of Required Authorization	81
2. Waiver of Authorization for Research.....	81
E. INFORMATION NEEDED FOR REVIEW.....	82
F. HUMAN SUBJECTS’ RIGHTS	83
1. Right to an Accounting	83
2. Right to Revoke Authorization	83
G. SUBJECT RECRUITMENT	83
1. Recruitment is Subject to the General Authorization Requirements.....	83
2. Requirements to Disclose PHI Contained in a Limited Data Set or as De-Identified Data.....	84
3. Limitations on Use of PHI in a Limited Data Set for Subject Recruitment.....	84
4. Recruiting Subjects Identified using their PHI	84
H. REQUIREMENTS FOR SECURITY OF PROTECTED HEALTH INFORMATION UNDER THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA).....	84
1. HITECH Act of 2009	85
2. Strengthened Enforcement Measures	85
XV. ELIGIBILITY FOR THE TITLE OF PRINCIPAL INVESTIGATOR ON PROTOCOLS.....	87
A. ELIGIBILITY FOR TITLE OF PRINCIPAL INVESTIGATOR ON PROTOCOLS.....	87
B. ADDITIONAL PRINCIPAL INVESTIGATOR CREDENTIALS REQUIRED BY FDA	88

C. EXCEPTIONS REQUIRING APPROVAL BY THE EXECUTIVE VICE PRESIDENT FOR RESEARCH.....	88
D. ELIGIBILITY EXCEPTIONS FOR GRADUATE AND UNDERGRADUATE STUDENTS AS PRINCIPAL INVESTIGATORS	89
1. <i>Exception for Georgia Tech Students Receiving Stipends and Tuition in Support of Their Work on Emory Protocols</i>	<i>89</i>
2. <i>Exception for Georgia Tech Students Receiving Fellowships Supporting Their Work on Emory Protocols</i>	<i>89</i>
E. CIRCUMSTANCES THAT RENDER RESEARCHER INELIGIBLE TO HOLD ROLE OF PRINCIPAL INVESTIGATOR, CO-PRINCIPAL INVESTIGATOR, OR INVESTIGATOR.....	90
F. DEFINITIONS.....	90
1. <i>Principal Investigator</i>	<i>90</i>
2. <i>Co-Principal Investigator.....</i>	<i>91</i>
3. <i>Co-Investigator</i>	<i>91</i>
XVI. RESEARCH IN INTERNATIONAL SETTINGS.....	92
FDA EXPORT CERTIFICATES.....	92
EXPORT CONTROL	92
XVII. OTHER AGREEMENTS, ISSUES, AND REVIEWS FOR YOUR CONSIDERATION.....	93
A. BIOLOGICAL MATERIAL SAFEGUARDS COMMITTEE (BSMC)	93
B. BUSINESS ASSOCIATE AGREEMENT (BAA)	93
C. CLINICAL TRIAL AGREEMENTS (CTA)	93
D. DATA USE AGREEMENT (DUA)	94
E. INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)	94
F. INSTITUTIONAL BIOSAFETY COMMITTEE (IBC).....	94
G. INSURANCE	94
H. LICENSING	94
I. LOAN EQUIPMENT AGREEMENTS	95
J. MATERIAL TRANSFER AGREEMENT (MTA)	95
XVIII. NON-GEORGIA TECH PERSONNEL (INCLUDING VISITING SCHOLARS AND MINORS) PARTICIPATING IN CONDUCT OF PROTOCOLS AT GEORGIA TECH	96
A. PARTICIPATION OF MINORS AS EMPLOYEES OR VOLUNTEERS IN LABORATORY AND OTHER ACTIVITIES RELATED TO HUMAN SUBJECTS RESEARCH	96
XIX. ADVERSE EVENTS AND UNANTICIPATED PROBLEMS.....	98
A. ADVERSE EVENTS.....	98
1. <i>Serious Adverse Events</i>	<i>99</i>
2. <i>Unanticipated Adverse Events</i>	<i>99</i>
3. <i>Unanticipated Adverse Device Effects (UADEs)</i>	<i>100</i>
4. <i>When Adverse Events Must Be Reported.....</i>	<i>100</i>
B. UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS OR OTHERS (UPIRTSO).....	101
1. <i>Requirement for Investigators to Report Unanticipated Problems.....</i>	<i>101</i>
2. <i>Requirement for Investigators to Monitor Problems.....</i>	<i>102</i>
C. INSTITUTIONAL REVIEW BOARD RESPONSE TO REPORTS OF ADVERSE EVENTS AND UNANTICIPATED PROBLEMS.....	102
D. INCIDENTAL FINDINGS.....	103
APPENDICES	105

APPENDIX 1: INVESTIGATOR AGREEMENT.....	107
APPENDIX 2: DATA STORAGE GUIDELINES AND RESOURCES	113
APPENDIX 3: ADDITIONAL REQUIREMENTS FOR RESEARCH INVOLVING DEPARTMENT OF DEFENSE, INCORPORATED BY ADDENDA TO FEDERALWIDE ASSURANCE	114
<i>A. Human Subjects Research as Defined by the DoD.....</i>	<i>114</i>
<i>B. Specific DoD Requirements.....</i>	<i>116</i>
<i>1. EDUCATION</i>	<i>116</i>
<i>2. SCIENTIFIC REVIEW</i>	<i>117</i>
<i>3. ACTIVE DUTY MILITARY--PROTECTIONS AGAINST UNDUE INFLUENCE</i>	<i>117</i>
<i>4. PROVISIONS FOR RESEARCH-RELATED INJURY</i>	<i>118</i>
<i>5. REPORTING UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS AND OTHERS (UPIRTSOs), INCLUDING ADVERSE EVENTS, AND RESEARCH RELATED INJURY</i>	<i>118</i>
<i>6. RESEARCH MONITOR</i>	<i>118</i>
<i>7. ADDITIONAL SAFEGUARDS FOR RESEARCH CONDUCTED WITH INTERNATIONAL POPULATIONS</i>	<i>120</i>
<i>8. WAIVER OF CONSENT</i>	<i>120</i>
<i>9. RESEARCH INVOLVING MINORS</i>	<i>121</i>
<i>10. LIMITATIONS ON COMPENSATION FOR U. S. MILITARY PERSONNEL</i>	<i>121</i>
<i>11. SURVEY RESEARCH.....</i>	<i>122</i>
<i>12. DRUGS, DEVICES AND BIOLOGICS, INVESTIGATIONAL TEST ARTICLES.....</i>	<i>122</i>
<i>13. PRISONERS OF WAR (POW), OTHER PRISONERS, AND DETAINEES.....</i>	<i>123</i>
<i>14. ALLEGATIONS OF NON-COMPLIANCE WITH HUMAN RESEARCH PROTECTIONS</i>	<i>124</i>
<i>15. CONFLICTING AND COMPETING INTERESTS.....</i>	<i>124</i>
<i>16. DOCUMENTATION AND OVERSIGHT THROUGH HEADQUARTERS-LEVEL REVIEW OF RESEARCH PROTOCOLS</i>	<i>125</i>
<i>17. AUDITS, INVESTIGATIONS OR INSPECTIONS OF DEPARTMENT OF NAVY-SUPPORTED RESEARCH.....</i>	<i>126</i>
<i>18. PUBLICATIONS, PRESENTATIONS OR REPORTS BASED ON THE RESEARCH PROTOCOL.....</i>	<i>126</i>
<i>19. STUDY CLOSURE:.....</i>	<i>127</i>
<i>20. RECORD RETENTION:</i>	<i>127</i>
<i>21. PRINCIPAL INVESTIGATOR ACTIONS:.....</i>	<i>127</i>
APPENDIX 4: SCIENTIFIC REVIEW TEMPLATE FOR DOD PROTOCOLS.....	129
APPENDIX 5: NANOTECHNOLOGY GUIDANCE.....	131
APPENDIX 6: FDA GUIDANCE FOR SPONSORS, CLINICAL INVESTIGATORS, AND IRBs REGARDING FDA FORM 1572	136
<i>ATTACHMENT A: COPY OF FORM 1572</i>	<i>146</i>
<i>ATTACHMENT B: INVESTIGATOR RESPONSIBILITIES FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS</i>	<i>149</i>
APPENDIX 7: FREQUENTLY ASKED QUESTIONS, STATEMENT OF INVESTIGATOR (FORM FDA 1572)	153
APPENDIX 8: FDA DRAFT GUIDANCE FOR INDUSTRY AND FDA ADMINISTRATION STAFF – INVESTIGATIONAL DEVICE EXEMPTIONS (IDE) FOR EARLY FEASIBILITY MEDICAL DEVICE CLINICAL STUDIES, INCLUDING CERTAIN FIRST IN HUMAN (FIH) STUDIES.....	171
APPENDIX 9: FDA GUIDANCE FOR CLINICAL INVESTIGATORS, SPONSORS, AND IRBs: INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) – DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AND IND.....	197
APPENDIX 10: GEORGIA TECH REGULATORY AFFAIRS OFFICE CLINICALTRIALS.GOV INITIAL QUESTIONS DOCUMENT.....	224
APPENDIX 11: GEORGIA TECH REGULATORY AFFAIRS OFFICE CLINICALTRIALS.GOV INVESTIGATIONAL QUESTIONS DOCUMENT	230

**APPENDIX 12: GEORGIA TECH REGULATORY AFFAIRS OFFICE CLINICALTRIALS.GOV
OBSERVATIONAL QUESTIONS DOCUMENT 232**
GLOSSARY 234

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

I. Mission

Revised: July 2022

Georgia Institute of Technology’s Regulatory Affairs and Clinical Trials office is charged with the responsibility to ensure that the appropriate laws and regulations are being followed when research is conducted with an FDA regulated product. The Regulatory Affairs and Clinical Trials office is also charged with ensuring that the appropriate laws and regulations are being followed for all clinical trials taking place at Georgia Tech. These missions directly support the institute’s strategic plan, with particular emphasis on the strategic goals to “Amplify Impact” and “Champion Innovation.”

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

**II. Regulatory Affairs and Clinical
Trials Office Operations**

Reviewed: July 2022

To achieve its mission, the Regulatory Affairs and Clinical Trials office will perform multiple tasks. These tasks include reviewing research proposals that involve the use of FDA regulated products, assisting the Institutional Review Board in their review of FDA regulated research, ensuring that all study teams are compliant with the FDA laws and regulations, managing clinical trial submissions for the Institute, and ensuring all clinical trials taking place at Georgia Tech are compliant with the laws and regulations.

The Food and Drug Administration (FDA) frequently issues new guidance and regulation revisions; thus, the Regulatory Affairs and Clinical Trials office will take into account current regulatory guidance in its review of any device, drug, biologic, or combination product studies.

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

**III. Statutory Basis of Regulatory
Affairs and Clinical Trials Office
Authority**

Revised: July 2022

The Regulatory Affairs and Clinical Trials office is an administrative body established to ensure that all research activities involving FDA regulated products conducted under the auspices of the Georgia Institute of Technology are compliant with the Federal Food, Drug and Cosmetic Act and subsequent amending statutes which are codified in Title 21 Chapter 9 of the United States Code.

The Georgia Tech Regulatory Affairs and Clinical Trial office as part of the Human Research Protection Program is subject to regulation and inspection, as provided in the regulations cited below.

A. Department of Health and Human Services (DHHS)

DHHS regulations pertaining to rights and welfare of subjects participating in research supported with federal funding are specified in *Title 45 Code of Federal Regulations Part 46*, “Federal Policy for the Protection of Human Subjects” and including *Subparts A, B, C, and D*.

B. Food and Drug Administration (FDA)

FDA regulations pertaining to rights and welfare of subjects participating in research involving drugs, medical devices, and biological products and other products regulated by the FDA are specified in *Title 21 Code of Federal Regulations, Parts 50* Protection of Human Subjects, *56* Institutional Review Boards, *312* Investigational New Drug Application, and *812* Investigational Device Exemptions. See *Appendix 21* for FDA guidance on the responsibilities of researchers conducting work subject to FDA.

C. State of Georgia

1. Prisoner Studies

Medical experiments involving prisoners require prior written approval of the Commissioner of Corrections. Ga. Comp. R. & Regs. 125-4-4-.12.

2. Genetic Research

Genetic information is the unique property of the individual. Its use may be abused if disclosed to unauthorized third parties without consent. Official Code of Georgia Annotated 33-54-1. Definition of "genetic testing." Ga.Code 33-54-2. Informed consent required prior to genetic testing for insurance reasons. Ga.Code 33-54-3. Genetic information may be released only to the individual tested or authorized persons or to a third party with explicit written consent. Ga.Code 33-54-3. Insurers may not use genetic information for nontherapeutic purposes. Ga.Code 33-54-4 (but see Ga.Code 33-54-7). Research facilities may conduct genetic testing and use the information for scientific research purposes if the individual's identity is not disclosed. Ga.Code 33-54-6.

3. Consent Age

The State of Georgia defines minors as those persons under the age of 18 years. Emancipated minors may participate in some studies otherwise unsuitable for children, provided adequate justification. *Note that in its definition of children in clinical research, the National Institutes of Health, effective 2016, states that "...for the purposes of inclusion policy, the age of a child will be defined as individuals under 18 years old instead of under 21 years old."*

4. Controlled Substances

Persons who handle controlled substances or dangerous drugs for the purpose of conducting research, and who are not registered as a pharmacy, drug wholesaler, distributor, supplier or medical practitioner, must register biennially with the Board of Pharmacy and obtain a drug researcher permit. Official Code of Georgia Annotated 26-4-49. The registered person must maintain accurate records of purchase, receipt, use, and disposal of the drugs for at least two years. Ga.Code 26-4-49. A copy of the researcher's controlled substances permit may be requested by the Office of Research Integrity Assurance in some situations.

5. Phase II and III Cancer Clinical Trials

All State health plans in Georgia must reimburse the patient's "routine care" costs associated with a dependent child's participation in a phase II or phase III cancer clinical trial that is testing prescription drugs. The child has to have been diagnosed with cancer prior to his or her 19th birthday, and the trial has to have been approved by FDA or NCI. S.B. 603.

An approved clinical trial program under Ga Code 33-24-59.1 is defined as a clinical trial that:

- Tests new therapies, regimens, or combinations thereof against standard therapies or regimens for the treatment of cancer in children;
- Introduces a new therapy or regimen to treat recurrent cancer in children; or
- Seeks to discover new therapies or regimens for the treatment of cancer in children which are more cost effective than standard therapies or regimens; and
- Has been certified by and utilizes the standards for acceptable protocols established by the:
 - Pediatric Oncology Group;
 - Children's Cancer Group; or
 - Commissioner as he or she may otherwise define such term by rule and regulation after due notice, any required hearing, and compliance with any other requirements of applicable law, but only providing for such definition in a manner at least as restrictive as that established in this Code section.

6. Drug Investigation Laws

Investigational drugs may be used by scientific experts provided the drug is labeled "For Investigational Use Only." Official Code of Georgia Annotated 26-3-10. For outpatient clinics and hospital pharmacies, an investigational drug shall be administered under the direct supervision of the Principal Investigator or authorized clinician, with prior approval by a hospital committee, in accordance with an approved protocol and informed consent. Nurses shall be educated before administering the drug. The pharmacy shall maintain information on the drug. Patient confidentiality shall be maintained. Ga. Comp. R. & Regs. 480-13-.09, Ga. Comp. R. & Regs. 480-33-.09.

7. Medical and Other Records Privacy

Any hospital, health care facility or other organization rendering patient care may provide information, reports, statements, memoranda or other data relating to the condition and treatment of any person to research groups approved by the medical staff of the institution, to be used in any study to reduce morbidity or mortality rates so long as the identity of the patient remains confidential. Official Code of Georgia Annotated 31-7-6.

Vital records may be disclosed for research purposes. Ga.Code 31-10-25; Ga. Comp. R. & Regs 290-1-3-.33.

Physicians, hospitals and health care facilities are not required to release raw medical data used in research except where authorized by law or by the patient or guardian. Ga.Code 24-9-40. The legislature declares that protecting the confidentiality of research data is essential to safeguarding the integrity of research. Defines "confidential raw research data" as that provided in support of a study approved by an oversight committee of a hospital, health care facility or educational institution, where the subjects' identities will not be material to the results, and will not be disclosed except to the subject or with the subject's written authorization or to a research sponsor. Ga.Code 24-9-40.2. Records must be furnished within a reasonable period of time to the patient, a provider designated by the patient or any other person designated by the patient. Ga.Code 31-33-2. Fees for search, retrieval and other direct administrative costs related to the provision of patient records established; may be adjusted annually by the state Office of Planning and Budget in accordance with the medical component of the consumer price index. All records remain the property of the provider. Ga.Code 31-33-3.

8. STD Reporting

HIV/AIDS information is confidential and shall not be disclosed except with the patient's consent. Physicians may inform the spouse, sexual partner or child if they are at risk of being infected and the physician attempted to notify the patient of the disclosure. Official Code of Georgia Annotated 24-9-40.1, Ga. Code 24-9-47. Health care providers, health care facilities or other persons who order an HIV test shall report each positive result to the Dept. of Health, along with information on patient's age, sex, race, address. Ga. Code 31-22-9.2. HIV tests may be ordered only after counseling the person, which may include information on AIDS, transmission, confidentiality, medical treatment. Ga. Code 31-22-9.2, Definitions Ga. Code 31-22-9.1. Minors may consent to treatment of STDs. Information may be given to or withheld from parents in the physician's judgment. Ga. Code 31-17-7. Any physician, hospital manager or other person who diagnoses or treats a case of venereal disease shall report it to the Dept. of Health. Ga. Code 31-17-2; Ga. Comp. R & Regs. 290-5-17-.02. Labs shall comply with reporting requirements for STDs unless operated exclusively for research purposes. Ga. Code 31-17-6, Ga. Code 31-22-9.

D. Health Insurance Portability and Accountability Act (HIPAA)

The Department of Health and Human Services' *National Standards to Protect the Privacy of Personal Health Information* are promulgated in the Health

Insurance Portability and Accountability Act (HIPAA), commonly referred to as the “Privacy Act.” This Act specifies requirements for protection of individually identifiable health information, or “protected health information” (PHI). See Section XIV of these policies, “*Health Insurance Portability and Accountability Act (HIPAA) for Protected Health Information,*” for a complete discussion of HIPAA and the procedures to comply at Georgia Tech.

E. Department of Defense, Incorporated by Addenda to Federalwide Assurance

An Addendum to Georgia Tech’s Federalwide Assurance incorporates the Department of Defense’s additional requirements for human subjects research involving the DOD. The Addendum documents Georgia Institute of Technology’s assurance that it shall comply with the following laws, regulations, and guidance when conducting, reviewing, approving, overseeing, supporting, or managing DoD-supported research with human subjects:

- The Belmont Report
- Title 32 Code of Federal Regulations Part 219 (32 CFR 219), Department of Defense Regulations, “Protection of Human Subjects”
- Title 45 Code of Federal Regulations Part 46, (45 CFR 46) Department of Health and Human Services Regulations, “Protection of Human Subjects,” Subparts B, C, and D as made applicable by DoDD 3216.02
- Title 21 Code of Federal Regulations 50, 56, 312, and 812, Food and Drug Administration (FDA) Regulations
- DoD Directive (DoDD) 3216.02, “Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research”
- Title 10 United States Code Section 980 (10 USC 980), “Limitation on Use of Humans as Experimental Subjects”
- DoDD 3210.7, “Research Integrity and Misconduct”
- DoDD 6200.2, “Use of Investigational New Drugs in Force Health Protection”
- Department of the Army
 - AR 70-25 Use of Volunteers as Subjects of Research, 25 January 1990
 - AR 40-38, Clinical Investigation Program, 1 September 1989
 - AR 40-7, Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances, 4 January 1991
- Department of the Navy
 - SECNAVINST 3900.39D of 6 November 2006
- Department of the Air Force
 - Air Force Instruction 40-402, Protection of Human Subjects in Research
- Office of the Secretary of Defense for Personnel and Readiness
 - HA Policy 05-003

- National Geospatial Intelligence Agency
- National Security Agency
- Defense Intelligence Agency
- Defense Threat Reduction Agency
- Defense Advanced Research Projects Agency
- United States Joint Forces Command
- Any other applicable requirements.

Appendix 2 sets forth the Department of Defense requirements in greater detail.

IV. Food & Drug Administration (FDA) Regulated Products

Reviewed: July 2022

The FDA regulates a variety of products, including but not limited to human and veterinary drugs, vaccines and other biological products, and medical devices intended for human use. These products are described in more detail below:

A medical device is defined by the Food and Drug Administration as *An instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent or similar or related article, including any component, part or accessory which is:*

- *Recognized in the official National Formulary or USP, or any supplement to them,*
- *Intended for use in diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in man or other animals, or*
- *Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes. [FDA 92-4173]*

A drug is defined by the Food and Drug Administration as:

- *A substance recognized by an official pharmacopoeia or formulary, or any supplement to any of them.*
- *A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.*
- *A substance (other than food) intended to affect the structure or any function of the body of man or other animals.*
- *A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.*

A biologic is defined by the Food and Drug Administration as:

- *A substance recognized by an official pharmacopoeia or formulary, or any supplement to any of them.*
- *A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.*

- *A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound).*

A combination product is defined by the Food and Drug Administration as a combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. Under 21 CFR 3.2 (e), a combination product is defined to include:

- 1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity [often referred to as a “single-entity” combination product];*
- 2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products [often referred to as a “co-packaged” combination product];*
- 3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose) [often referred to as a “cross-labeled” combination product]; or*
- 4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect [another type of “cross-labeled” combination product].*

V. Medical Device Research

Revised: December 2022

A. Research Involving the Use of Investigational Medical Devices

An Investigational Medical Device is defined by the FDA as *An instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent or similar or related article, including any component, part or accessory which is:*

- *Recognized in the official National Formulary or USP, or any supplement to them,*
- *Intended for use in diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in man or other animals, or*
- *Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes. [FDA 92-4173]*

Research involving investigational medical devices requires approval from the FDA through a process known as Investigational Device Exemption (IDE). In this process, the study team is still required to comply with specific FDA regulations including but not limited to the IDE regulations (§21CFR812; section C of this policy) and Quality System Regulations (§21CFR 820; section I of the policy). However, the study team and the device are exempt from other regulations that would normally be imposed.

Investigational medical devices may be reviewed under the Abbreviated IDE requirements (§21CFR812.2b) where the Institutional Review Board (IRB) acts in place of the FDA. Devices that fall under these categories do not require a submission to the FDA prior to the clinical investigation, only to the IRB. Furthermore, these devices are exempt from some, but not all IDE regulations. More detail is provided in section C of this policy.

Lastly, some scenarios are exempt from the IDE regulations as set forth in 21CFR812. Devices that fit these very specific categories do not need to comply with the IDE regulations. However, these devices may still have to comply with specific FDA regulations that pertain to them. More information can be found in section C of this policy.

All IDEs and Abbreviated IDEs require Institutional Review Board (IRB) approval prior to the investigation taking place with human subjects (§21CFR812). Informed consent (§21CFR50) and other specific criteria such as IRB approval to ensure that the risks to the subjects are reasonable in relation to the anticipated benefits are required by the FDA for approval (§21CFR56).

B. Checklist for Studies Involving Investigational Devices:

All protocols that propose testing of investigational devices must satisfactorily address the following points:

- Study Title with Number and Revision Level
- Investigator Credentials, including Medical and State/Federal Licenses, As Required
- Investigational Sites
- Clinical Background of Condition Being Studied
- Study Objective
- Risk Determination (NSR/SR)
- Device Description
 - Description
 - Principles of operation
 - Components and Materials
 - Manufacturing Information
 - Device labels
 - Instructions for Use
 - Operations Manual
 - Import/Export Information
- Report of Prior Investigations
 - Animal Studies
 - Prior Human Studies
 - Bench testing description regarding safety
- Study Design
- Study Population
 - Inclusion/Exclusion Criteria
 - Recruitment Plan
- Study Procedures
- Study Visit Schedule
- Case Report Forms
- Data Collection and Reporting
- Ethical Considerations
 - Human Subjects Protection

- Informed Consent Form
- Safety Updates, Any New Information
- Protocol Amendments
- Retention of Records
- Use of Information and Publication
- Statistical Justification and Data Analysis Plan
- Risks and Benefits Analysis
- Safety Assessment
- Data Disclosure and Subject Confidentiality
- Study Monitoring Plan

C. Determining the Safety or Effectiveness of a Device

When a study is designed to evaluate the safety or effectiveness of a device, the convened IRB or the Office of Research Integrity Assurance (if the device fits the criteria to be IDE Exempt) will confirm and document either that:

1. The device has a valid IDE number. The IDE for each device must be supported by one of the following:
 - The sponsor protocol imprinted with the IDE number;
 - A written communication from the sponsor documenting the IDE number;
 - A written communication from the FDA documenting the IDE number (required if an investigator listed on this protocol holds the IDE).

OR

2. The device fulfills the requirements for an abbreviated IDE [§21CFR812.2(b)(1)]
 - The device is not a banned device;
 - The device is labeled by the sponsor in accordance with the FDA Investigational Device Exemptions at §21CFR812.5;
 - The sponsor will obtain 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;
 - The sponsor will ensure that each investigator participating in the investigation of the device obtains from each subject under the investigator's care, consent as required by FDA Regulations on the Protection of Human Subjects (§21CFR50) and documents it;
 - The sponsor will comply with the requirements of the FDA Investigational Device Exemptions at §21CFR812.46 with respect to monitoring investigations;
 - The sponsor will maintain the records required under the FDA Investigational Device Exemptions at §21CFR812.140(b) (4) and (5)

and makes the reports required under the FDA Investigational Device Exemptions at §21CFR812.150(b) (1) through (3) and (5) through (10);

- The sponsor will ensure that participating investigators maintain the records required by the FDA Investigational Device Exemptions at §21CFR4 812.140(a)(3)(i) and make the reports required under §21CFR812.150(a) (1), (2), (5), and (7); and
- The sponsor complies with the prohibitions in the FDA Investigational Device Exemptions at §21CFR812.7 against promotion and other practices.

OR

3. The device fulfills one of the IDE exemption categories §21CFR812.2(c):

A. The device, other than a transitional device, was introduced into commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time;

B. The device, other than a transitional device, was introduced into commercial distribution on or after May 28, 1976, that FDA had determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that was used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence;

C. The device is a diagnostic device and the sponsor will comply with applicable requirements in §21CFR809.10(c) and the testing:

- Is noninvasive;
- Does not require an invasive sampling procedure that presents significant risk;
- Does not by design or intention introduce energy into a participant;
- Was not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure;

D. The device is undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing was not for the purpose of determining safety or effectiveness and does not put participants at risk;

E. The device is intended solely for veterinary use;

F. The device is shipped solely for research on or with laboratory animals and labeled in accordance with the FDA Investigational Device Exemptions at §21CFR812.5(c);

G. The device is a custom device as defined in the FDA Investigational Device Exemptions at §21CFR812.3(b) and is not being used to determine safety or effectiveness for commercial distribution.

D. FDA Device Classification

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.

1. The Three Device Classes and Related Requirements

- a. Class I General Controls
 - With Exemptions
 - Without Exemptions
- b. Class II General Controls and Special Controls
 - With Exemptions
 - Without Exemptions
- c. Class III General Controls and Premarket Approval

The class to which a device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If a device is classified as Class I or II, and if it is not exempt, a 510k will be required for marketing. All devices classified as exempt are subject to the limitations on exemptions. Limitations of device exemptions are covered under §21CFR Parts 862-892. For Class III devices, a premarket approval application (PMA) will be required unless the device is a pre-amendment device (that is, it was on the market prior to 1976, or is substantially equivalent to such a device) and PMAs have not been called for. In that case, a 510k will be the route to market.

Device classification depends on the *intended use* of the device and also upon *indications for use*. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea". Indications for use can be found in the device's labeling, but may also be conveyed orally during sale of the product.

In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

As indicated above all classes of devices are subject to General Controls. General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II, and III.

2. How to Determine Classification

To find the classification of a device, as well as whether any exemptions may exist, the regulation number for the device must be identified. There are two methods for accomplishing this: go directly to the [classification database](#) and search for a part of the device name, or, if you know the [device panel](#) (medical specialty) to which your device belongs, go directly to the listing for that panel and identify your device and the corresponding regulation. You may make a choice now, or continue to read the background information below. If you continue to read, you will have another chance to go to these destinations.

If you already know the appropriate panel you can go directly to the CFR and find the classification for your device by reading through the list of classified devices, or if you're not sure, you can use the keyword directory in the [PRODUCT CODE CLASSIFICATION DATABASE](#). In most cases this database will identify the classification regulation in the CFR. You can also check the [classification regulations](#) below for information on various products and how they are regulated by CDRH. Each classification panel in the CFR begins with a list of devices classified in that panel. Each classified device has a 7-digit number associated with it, e.g., [§21CFR880.2920](#) - Clinical Mercury Thermometer. Once you find your device in the panel's beginning list, go to the section indicated: in this example, [§21CFR880.2920](#). It describes the device and says it is Class II. Similarly, in the Classification Database under "thermometer", you'll see several entries for various types of thermometers. The three letter product code, FLK in the database for Clinical Mercury Thermometer, is also the classification number which is used on the Medical Device Listing form.

Once you have identified the correct classification regulation go to [What are the Classification Panels](#) below and click on the correct classification regulation or go to the [CFR Search page](#). Some Class I devices are exempt from the premarket notification and/or parts of the good manufacturing practices regulations. Approximately 74% of the Class I devices are exempt from the premarket notification process. These

exemptions are listed in the classification regulations of §21CFR and also has been collected together in the [Medical Device Exemptions](#) document.

E. Determination of Significant and Nonsignificant Risk in Medical Device Studies

The regulations at §21CFR812 discuss Investigational Device Exemptions which include two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). The risk determination has important implications for researchers. Nonsignificant risk device studies have fewer regulatory controls than do SR studies and are governed by the abbreviated requirements [§21CFR812.2(b)].

1. Two Types of Device Studies

a. Significant Risk Device

An SR device study is defined as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and

- (i). is intended as an implant; or
- (ii). is used in supporting or sustaining human life;

or

- (iii). is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
- (iv) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

b. Nonsignificant Risk Device

An NSR device investigation is one that does not meet the definition for a significant risk study. *NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [§21CFRPart 56] to identify certain studies that may be approved through an "expedited review" procedure.* For both SR and NSR device studies, IRB approval is required prior to conducting clinical trials, and continuing review by the IRB is required. In addition, informed consent must be obtained for both types of studies; the Food & Drug Administration's regulations do not allow for a waiver of consent.

2. Implications of Differences in Significant and Nonsignificant Risk Devices

There are major differences in the approval process and in the record keeping and reporting requirements for SR and NSR studies. The

SR/NSR decision is also important to the Food and Drug Administration (FDA) because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

If an IRB believes that a device study is significant risk, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination.

The assessment of whether a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application. The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, severely debilitating, could result in permanent impairment of a body function or permanent damage

to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining whether a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

An investigation of a device submitted to FDA for risk determination may not begin until 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 until FDA approves, by order, an IDE for the investigation.

a. Nonsignificant Risk IDE 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.

b. Significant Risk IDE Requirements

When the IRB determines that a device is “Significant Risk” (per 812.66), the Investigational Device Exemption (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.

F. Device Label

As part of the protocol submission, investigators must provide a complete label that will be affixed to the device. This label must comply the criteria set forth in the Labeling of Investigational Devices section (§21CFR812.5) or the Labeling for In Vitro Diagnostic Products (IVD) (§21CFR809.10), depending on what kind of device is being tested.

For the purposes of this policy, only the “label” of investigational products will be discussed. The Institute is mainly only focused on research, and therefore labeling for products being marketed will not be discussed. If a study team intends to market a device, the study team must meet with the Office of Research Integrity Assurance to discuss all of the specific regulations that apply.

1. Definitions of Label and Labeling

The Federal Food, Drug and Cosmetic Act (FFDCA) defines a label as the 'display of written, printed, or graphic matter upon the immediate container of any article...' (section 201 (k)). The term 'immediate

container' does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear 'on the outside container or wrapper, if any there be, or the retail package of such article, or is easily legible through the outside container of wrapper.'

The same section of FFDCFA defines 'labeling' as 'all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article' at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce (Section 201(m)). The term 'accompanying' is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. 'Accompanying' also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.

2. Device Label for an IDE and Abbreviated IDE

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. (§21CFR812.5)

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. (§21CFR812.5)

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." (§21CFR812.5)

d. Exceptions or Alternatives

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. (§21CFR812.5)

3. Device Label for an IVD

In Vitro Diagnostics (IVD) have very specific label requirements that differ from the IDE label requirements. These requirements are found in the Code of Regulations (§21CFR809.10) and are very extensive. The requirements cover specific rules and situations including but not limited to IVDs for research use only, reagents, instruments, and general purpose reagents and equipment. Due to the complexity of these regulations, we recommend that research teams using an IVD meet with the Office of Research Integrity Assurance to discuss what is required for the specific product in question.

G. Control, Handling and Documentation of Devices Used in Investigations

As part of the protocol submission, investigators must provide a description of the planned process for control, handling and documentation of devices investigated or evaluated in the proposed research study. A member of the IRB will evaluate whether the proposed plan is adequate.

H. Case Report Forms

As the principal mechanism for clinical trials data collection, Case Report Forms (CRFs) can directly affect the success or failure of a clinical trial. The information captured in CRFs is used to evaluate each question posed by the study. *The clinical trial sponsor (sponsor-investigator) is responsible for developing an appropriate CRF for the clinical trial in which it will be used.* CRFs must be finalized before data collection begins and should:

- Collect data with all users in mind;
- Collect data required by the regulatory agencies;
- Collect data outlined in the protocol;
- Be concise and clear as to meaning;
- Avoid duplication;
- Allow for minimal free-text responses;
- Provide units to ensure comparable values;
- Provide instructions to reduce misinterpretations

- Provide choices for each question;
- Allow for “*none*” and “*not done*” as responses; and
- Collect data in a manner that supports efficient computerization.

I. Quality Systems Regulations (§21CFR820)

Quality Systems Regulations (QSR) refer to a set of regulations outlined in §21CFR820. These regulations discuss many areas in regards to design controls, productions controls, records, and many other areas. Most of the QSR apply to finished medical devices that are ready to be manufactured in the market. Other than Design Controls, this section does not apply to devices that are only undergoing research testing at or by Georgia Tech investigators.

If a study team intends to test their device in clinical trials and eventually seek market approval or clearance, then the study team should become familiar with the design controls outlined in §21CFR820.30. This section of the regulations discusses controls in regards to design input, design output, design review, design verification, design validation, design transfer, design changes, and the design history file. It is highly suggested to meet with the ORIA staff to discuss these regulations if you intend to bring your device to market, as there are both guidance documents and regulations regarding design controls that need to be complied with.

J. Responsibilities of All Investigators Conducting Research Subject to the FDA Regulations (§21CFR812.100)

Investigators have numerous responsibilities when conducting research subject to the FDA regulations, including:

- Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation.
- Conducting the investigation in accordance with:
 - the signed agreement with the sponsor
 - the investigational plan
 - the regulations set forth in §21CFR812 and all other applicable FDA regulations, and
 - any conditions of approval imposed by an IRB or FDA
- Supervising the use of the investigational device. 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 §21CFR812 to receive it.

- 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 under Part 54.
- Disposing of the device properly. 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.

1. Maintaining Records (§21CFR812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

- a. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA
- b. Records of receipt, use or disposition of a device that relate to:
 - (1) the type and quantity of the device, dates of receipt, and batch numbers or code marks
 - (2) names of all persons who received, used, or disposed of each device
 - (3) the number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore
- c. Records of each subject's case history and exposure to the device, including:
 - (1) 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
 - (2) justifying the failure to obtain informed consent
 - (3) document all relevant observations, including records concerning adverse device effects (whether anticipated or not), 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
 - (4) a record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy

- d. The protocol, with documents showing the dates of and reasons for each deviation from the protocol
- e. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

2. Inspections

(§21CFR812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.

3. Submitting Reports

(§21CFR812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

- a. To the sponsor and the IRB:
 - (1) Any unanticipated adverse device effect occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)
 - (2) Progress reports on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)
 - (3) Any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)
 - (4) Any use of the device without obtaining informed consent. (Due within 5 working days after such use.)
 - (5) A final report. (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")
 - (6) Any further information requested by FDA or the IRB about any aspect of the investigation.
- b. To the Sponsor:

- (1) Withdrawal of IRB approval of the investigator's part of an investigation. (Due within 5 working days of such action).

4. Investigational Device Distribution and Tracking

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it (§21CFR812.110(c)). The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of the device(s).

Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (§21CFR812.110(e)).

Investigators must also maintain complete, current and accurate records of the receipt, use, or disposition of investigational devices (§21CFR812.140(a)(2)). Specific investigator recordkeeping requirements are set forth at §21CFR812.140(a).

5. Prohibition of Promotion and Other Practices

(§21CFR812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

- a. Promotion or test marketing of the investigational device
- b. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling
- c. Unduly prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective, and
- d. Representing that the device is safe or effective for the purposes for which it is being investigated.

6. Annual Progress Reports and Final Reports

The annual progress and final reports to the sponsor and the IRB must also include the following items:

- a. IDE number
- b. Device name
- c. Indications for use
- d. Brief summary of study progress in relation to investigational plan
- e. Number of investigators and investigational sites
- f. Number of subjects enrolled
- g. Number of devices received, used, and the final disposition of unused devices
- h. Brief summary of results and conclusions
- i. Summary of anticipated and unanticipated adverse device effects
- j. Description of any deviations from investigational plan
- k. Reprints of any articles published by the investigator in relation to the study

J. Additional Responsibilities of a Sponsor-Investigator

A sponsor-investigator, as defined in Food and Drug Administration regulations at §21CFR312.3 and 812.3(o), is an individual who both initiates and conducts a clinical investigation, and under whose immediate direction an investigational drug or device is administered, dispensed or used. A sponsor-investigator has the responsibilities usually assigned both to an investigator and to a sponsor. The IRB will evaluate whether the investigator is knowledgeable about the additional regulatory requirements for sponsors and may require additional oversight and monitoring of such studies to assure compliance with additional sponsor regulations.

Investigators must be trained to recognize device defects which occur from the improper performance of their specific jobs. 21 CFR 820.25(b)(2) states that personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions. The sponsor-investigator must provide acceptable evidence that such personnel are adequately trained

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

VI. Drug Research
Reviewed: July 2022

A drug is defined by the Food and Drug Administration as:

- *A substance recognized by an official pharmacopoeia or formulary, or any supplement to any of them.*
- *A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.*
- *A substance (other than food) intended to affect the structure or any function of the body of man or other animals.*
- *A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.*

Clinical research involving investigational or off-label drugs and certain biologics require an Investigational New Drug (IND) submission to the FDA. Investigators who contemplate research involving an investigational new drug submission (IND) must contact the Office of Research Integrity Assurance prior to preparation of such clinical research.

The following regulations apply to the IND application process:

21CFR Part 201	Drug Labeling
21CFR Part 312	Investigational New Drug Application
21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug
21CFR Part 316	Orphan Drugs
21CFR Part 50	Protection of Human Subjects
21CFR Part 54	Financial Disclosure by Clinical Investigators
21CFR Part 56	Institutional Review Boards
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- [Emergency Use IND](#) allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , [Sec. 312.23](#) or [Sec. 312.20](#). It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- [Treatment IND](#) is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in

humans. Also included are any previous experience with the drug in humans (often foreign use).

- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

<https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application>

VII. Biologics Research

Reviewed: July 2022

A biologic is defined by the Food and Drug Administration as:

- *A substance recognized by an official pharmacopoeia or formulary, or any supplement to any of them.*
- *A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.*
- *A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound).*

Research involving biologics may require a BLA or IND submission to the FDA. Investigators who contemplate research involving biologics must contact the Office of Research Integrity Assurance prior to preparation of such protocols.

Therapeutic biological products include:

- Monoclonal antibodies for in-vivo use
- Cytokines, growth factors, enzymes, immunomodulators; and thrombolytics
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunotherapies

<https://www.fda.gov/drugs/types-applications/therapeutic-biologics-applications-bla>

**VIII. Combination Products
Research**

Reviewed: July 2022

As defined in the FDA regulations at §21CFR3.2(e), a combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product. A combination product is defined to include:

1. A product comprising two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit comprising drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

When reviewing studies involving combination products, the IRB considers the Primary Mode of Action (PMOA), as defined in §21CFR3, in its review of the need for an IND and/or IDE for this Combination Product. When it is impossible to determine PMOA, *the primary therapeutic benefit* is considered by the IRB, which is ultimately guided by the FDA's determination of any IND/IDE requirements for the Combination Product.

Research involving combination products require a submission to the FDA. Investigators who contemplate research involving combination products must contact the Office of Research Integrity Assurance prior to preparation of such protocols.

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES AND PROCEDURES

**IX. Institutional Review Board
Requirements**

Reviewed: July 2022

A. General Provisions

This part contains the general standards for the composition, operation, and responsibility of an institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the 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. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations. ([§21CFR56.101\(a\)](#))

References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted. ([§21CFR56.101\(b\)](#))

1. Circumstances in Which IRB Review is Required
([§21CFR56.103](#))

Except as provided in 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

Except as provided in 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations

to submit the results of the investigation to the Food and Drug Administration.

2. Exemptions from IRB Requirement

(§21CFR56.104)

The following categories of clinical investigations are exempt from the requirements of IRB review:

1. Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.
2. Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.
3. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.
4. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or 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.

3. Waiver of IRB Requirement

(§21CFR56.105)

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

B. Organization and Personnel

(§21CFR56.107)

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, 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 the 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 those subjects.

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.

Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

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.

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.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

C. IRB Functions and Operations

(§21CFR56.108)

The IRB must follow written procedures: (1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred

since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

The IRB must follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of: (1) Any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or (3) any suspension or termination of IRB approval.

Except when an expedited review procedure is used (see 56.110), review of proposed research must take place 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.

1. IRB Review of Research (§21CFR56.109)

The IRB reviews and has authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

The information given to subjects as part of informed consent is required to be in accordance with 50.25. The IRB may require that information, in addition to that specifically mentioned in 50.25, 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.

Documentation of informed consent is required to be in accordance with 50.27 of this chapter, except as follows:

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

2. The IRB may, for some or all subjects, find that the requirements in 50.24 of this chapter for an exception from informed consent for emergency research are met.

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

The IRB will 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 will 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. For investigations involving an exception to informed consent under 50.24 of this chapter, the IRB will promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification will include a statement of the reasons for the IRB's determination.

The IRB will conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and has the authority to observe or have a third party observe the consent process and the research.

The IRB will provide in writing to the sponsor of research involving an exception to informed consent under 50.24 of this chapter a copy of information that has been publicly disclosed under 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB will provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

When some or all of the subjects in a study are children, an IRB must determine that the research study is in compliance with part 50, subpart D of this chapter, at the time of its initial review of the research. When some or all of the subjects in a study that was ongoing on April 30, 2001, are children, an IRB must conduct a review of the research to determine compliance with part 50, subpart D of this chapter, either at the time of continuing review or, at the discretion of the IRB, at an earlier date.

2. Expedited Review for Certain Kinds of Research (§21CFR56.110)

The Food and Drug Administration has established, and published 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, through periodic republication in the Federal Register.

The 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 1 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 IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited review procedure set forth in 56.108(c).

When the IRB which uses an expedited review procedure, a method for keeping all members advised of research proposals which have been approved under the procedure will be utilized.

The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

3. Criteria for IRB Approval of Research (§21CFR56.111)

In order to approve research covered by these regulations the IRB will 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 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 that 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, handicapped, or 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 part 50.
5. Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.
6. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
7. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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

In order to approve research in which some or all of the subjects are children, the IRB will determine that all research is in compliance with part 50, subpart D of this chapter.

4. Review by Institution

(§21CFR56.112)

Research covered by these regulations that has been approved by the 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.

5. Suspension or Termination of IRB Approval of Research

(§21CFR56.113)

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval will include a statement of the reasons for the IRB's action and will be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

6. Cooperative Research (§21CFR56.114)

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

When relying on another institution, a “Shell Submission” must be submitted to the IRB so that this reliance is tracked by the IRB. The Shell Submission should provide the following:

- A brief description of how the Georgia Tech investigators are involved in the research.
- A brief description of what is taking place at Georgia Tech.
- If externally funded, the funding must be listed and the grant application or statement of work must be provided.
- A complete description of the FDA regulated product being tested.
- All approved study documents from the institution being relied on shall be uploaded to the submission.

Please note that the IRB may request for other relevant supporting documentation or information when relying on another IRB's determination.

D. Records and Reports (§21CFR56.115)

The institution, or where appropriate the IRB, prepares and maintains 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 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, a member of governing panel or board, stockholder, paid or unpaid consultant.
6. Written procedures for the IRB as required by 56.108 (a) and (b).
7. Statements of significant new findings provided to subjects, as required by 50.25.

The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

**X. Informed Consent
Requirements**

Reviewed: July 2022

A. General Requirements for Informed Consent

(§21CFR50.20)

Except as provided in 21 CFR part 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.

B. Exception from General Requirements

(§21CFR50.23)

- 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 follow-up 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 written certification of the determinations made by the investigator and an independent physician required in paragraph (e)(1) or (e)(2) of this section to the IRB and FDA 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.

C. Exception from Informed Consent Requirements for Emergency Research

(§21CFR50.24)

- 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 the 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.

D. Elements of Informed Consent
(§21CFR50.25)

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.

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.

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."

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.

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.

E. Documentation of Informed Consent (§21CFR50.27)

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.

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.

XI. Inclusion of Minors in Clinical Research

Reviewed: July 2022

In addition to other responsibilities assigned to the IRB under 21 CFR part 50 and part 56, the IRB must review clinical investigations involving children as subjects covered by subpart D of part 50 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. ([§21CFR50.50](#))

A. Clinical Investigations Not Involving Greater than Minimal Risk ([§21CFR50.51](#))

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:

1. No greater than minimal risk to children is presented; and
2. 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.

B. Clinical Investigations Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to Individual Subjects ([§21CFR50.52](#))

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 that:

1. The risk is justified by the anticipated benefit to the subjects;
2. 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
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

C. 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
(§21CFR50.53)

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 that:

1. The risk represents a minor increase over minimal risk;
2. 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;
3. 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
4. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

D. Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
(§21CFR50.54)

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:

1. The IRB finds 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
2. 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:

- a. That the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or
- b. 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.

E. Requirements for permission by parents or guardians and for assent by children
(§21CFR50.55)

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.

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.

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.

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.

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 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.

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

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

F. Wards

(§21CFR50.56)

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.

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.

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES AND PROCEDURES

XII. Required Training

Reviewed: July 2022

Completion of the Good Clinical Practice (GCP) Collaborative Institutional Training Initiative (CITI) course is required for all Georgia Tech investigators who will conduct research on a medical device, drug, biologic, or an in vitro diagnostic. GCP training is also needed if your study is funded by the NIH and you are conducting a clinical trial as defined by the NIH (more information listed below).

First time users should complete the initial courses; thereafter, users will complete the refresher courses every three years. The Office of Research Integrity Assurance is informed by email when a person associated with Georgia Tech completes certification requirements.

A. NIH GCP Training Requirement

NIH expects all NIH-funded clinical investigators and clinical trial staff who are involved in the design, conduct, oversight, or management of clinical trials to be trained in Good Clinical Practice (GCP).

Recipients of GCP training are expected to retain documentation of their training. GCP training should be refreshed at least every three years in order to stay up to date with regulations, standards, and guidelines.

1. Purpose

The principles of Good Clinical Practice (GCP) help assure the safety, integrity, and quality of clinical trials by addressing elements related to the design, conduct, and reporting of clinical trials. GCP training describes the responsibilities of investigators, sponsors, monitors, and IRBs in the conduct of clinical trials.

GCP training aims to ensure that:

- the rights, safety, and well-being of human subjects are protected
- clinical trials are conducted in accordance with approved plans with rigor and integrity
- data derived from clinical trials are reliable

- Training in GCP may be achieved through the Good Clinical Practice (GCP) CITI module.

B. Additional Training Requirements

1. IRB and IACUC Required Training

Additional training may be required depending on the specifics of your research, including but not limited to specific training requirements for human subjects research and animal research. Please contact the Georgia Tech IRB for human subjects research training requirements. Additionally, please contact the Georgia Tech IACUC for animal research training requirements.

2. DOD Required Training

The Department of Defense components impose an additional training requirement for all personnel conducting or reviewing research involving the Department of Defense. See Appendix 3 for details.

3. Training Requirement for Off-Campus Researchers

Off-campus researchers who completed CITI modules through another entity may forward their certificates to the Georgia Tech Office of Research Integrity Assurance (ORIA). If the completed training did not cover all of the required information, then ORIA may ask that you complete the Georgia Tech affiliated CITI training to ensure all of the required information has been covered.

4. Expired Training

The Office of Research Integrity Assurance will verify training status not only at the time of review, but also during periodic reviews and audits. During such review, Research Integrity Assurance will send a reminder to research team members whose training is not current (or is expiring within 30 days). The Office of Research Integrity Assurance will also notify any relevant committees of training deficiencies, who then may withhold approval until the training requirement is satisfied.

XIII. Clinical Trials

Revised: July 2022

Clinical Trials are specific types of studies that are required to be registered in a public registry, such as ClinicalTrials.gov. Investigators are required to register their study on ClinicalTrials.gov when their study meets the definition of a clinical trial. The definition of a clinical trial is found in several places, such as the Food and Drug Administration Amendments Act of 2007 (FDAAA) 801, the Final Rule (45 CFR part 11), and the NIH definition of a clinical trial. Failure to comply with these laws and regulations can result in civil and criminal penalties.

A. Definitions of a Clinical Trial

1. FDA Definition of an “Applicable Clinical Trial” (ACT)

Registration at ClinicalTrials.gov is required for trials that meet the FDAAA 801 definition of an “Applicable Clinical Trial”, which includes the following:

1. Controlled clinical investigations (other than phase 1 investigations) of any U.S. Food and Drug Administration (FDA)-regulated drug or biological product for any disease or condition.
2. Certain studies of FDA-regulated medical devices, excluding small clinical trials to determine feasibility and certain clinical trials to test prototype devices, but including FDA-required pediatric post-market surveillances of a device product.

Applicable clinical trials generally include interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

- The trial has one or more sites in the United States;
- The trial is conducted under an FDA investigational new drug application or investigational device exemption;
- The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research

2. NIH Definition of a Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

NIH applications/proposals involving clinical trials with due dates on or after January 25, 2018 must be submitted to an FOA or request for proposal (RFP) that explicitly states it will accept clinical trials.

a. Special Considerations for Training, Fellowship, and Career Development Awards

Institutional Training awards do not support clinical trials (with the exception of some D43 and K12 awards).

The NIH encourages fellows to receive training in clinical research, however, NIH supported fellows are not permitted to conduct a clinical trial independently.

Career Development awards may support either independent clinical trials or a mentored research training experience, depending on the FOA.

3. OHRP Final Rule Definition of a Clinical Trial

A federally funded research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

B. Process for Registering Clinical Trials on ClinicalTrials.gov

The “Sponsor” of the study is responsible for registering the trial in a public registry such as ClinicalTrials.gov. The Sponsor of industry-initiated and funded multi-center studies is the pharmaceutical or medical device company whose protocol you are following. For investigator-initiated studies from our faculty, Georgia Tech is considered the Sponsor and the Institute is therefore responsible for registering those studies. The Institute is a registered Sponsor at ClinicalTrials.gov. The personnel in ORIA’s Regulatory Affairs Office are listed as the designated administrators for the Institute’s ClinicalTrials.gov account.

The process for registering individual studies is described below. Remember, this pertains only to investigator-initiated studies.

1. A study must have been submitted to the IRB for review prior to registry although IRB approval will not be provided until the ClinicalTrials.gov NCT number has been received.
2. Georgia Tech's IRB does not review the data registered for a given trial. This review is performed by the Institute administrators for Georgia Tech's ClinicalTrials.gov account. However, ultimate responsibility for record accuracy lies with the Principal Investigator (PI) providing the requested details within Clinical Trails section of the IRB application.
3. An individual user account will need to be established at ClinicalTrials.gov by the Institute administrators for the Principal Investigator (PI) of the study and designees requiring record access. Send an e-mail to the administrators in the Regulatory Affairs Office providing the user's name, department, telephone number, and e-mail address. The user account will be created within ClinicalTrials.gov and within a very few minutes of the user account set-up, the new user will receive an e-mail from ClinicalTrials.gov providing the login details and temporary password.
4. The Institute administrators will enter specific information about the study that has been acquired from the IRB human subjects protocol application. The complete data set is described in the following document (ClinicalTrials.gov Database Requirements Document listed in [Appendix 10](#)). All of the information on this document is taken directly from the ClinicalTrials.gov website.
5. Once the information is entered and released by the Institute administrators, ClinicalTrials.gov will perform a system validation and quality assurance review. For protocol records this usually occurs within 2 to 5 days of release. For records containing results, this process may take up to 30 days. After completion of their review, ClinicalTrials.gov will assign an NCT number and make the record (or updates) publicly available for viewing. Until this occurs, no one outside of Georgia Tech can see the record or updated information. A study is not considered to be registered until the QA process has been completed and the NCT number has been assigned. Please allow adequate time for this process.

In order to qualify for publication consideration, enrollment shall not begin until this entire process has been completed.

C. Maintenance of Clinical Trials

The Principal Investigator is responsible for maintaining the accuracy of the information on the registered trial. This includes updating the information as appropriate, minimally every 6 months or whenever a significant change occurs, and noting when enrollment ceases. This information should be provided directly to the Institute administrators.

D. Submitting Consent Forms

The FDA, NIH and OHRP require consent forms that were used in the research to be posted within 60 days after the last study visit by the last participant.

For clinical trials defined by the NIH or under FDAAA 801, the consent form must be posted in the clinicaltrials.gov system under the clinical trial registration. In order to comply with this regulation, the Principal Investigator of the clinical trial is required to inform the Regulatory Affairs staff that enrollment is closed within 60 days of the last participant's last study visit. Once notified, the Regulatory Affairs staff will upload the consent form that is listed in the IRB submission system to clinicaltrials.gov.

For clinical trials defined by OHRP (45 CFR 46) and do not meet the definition of a clinical trial by the NIH or under FDAAA 801, the awardee must post a consent form that was used in the study to one of two federal websites within 60 days after the last participant's study visit. The Regulatory Affairs staff will be responsible for posting the consent form to the federal website. Therefore, in order to comply with this requirement, study teams who are conducting clinical trials as defined by 45 CFR 46 must inform the Regulatory Affairs staff that the enrollment is closed within 60 days of the last participant's last study visit. Once notified, the Regulatory Affairs staff will upload the consent form that is listed in the IRB submission system to one of the designated federal websites.

E. Submitting Clinical Trial Results

The Principal Investigator is responsible for posting clinical trial results for the registered trial. The results include sections such as Participant Flow, Baseline Characteristics, Outcome Measures and Statistical Analysis, Adverse Events, and the Protocol and Statistical Analysis Plan. This information should be entered by the Principal Investigator. Once the results have been entered and the documents uploaded, The Principal Investigator is asked to notify the

Regulatory Affairs staff, as this should be released to the PRS system by the Institute administrators.

Results are required to be made public 1 year after the study completion date. Additionally, the review process for clinical trial results can take several months. Therefore, the Principal Investigator is asked to submit the results as soon as possible following the study completion date to satisfy this requirement.

**XIV. Health Insurance Portability
and Accountability Act (HIPAA)
for Protected Health Information**

Revised: July 2022

Personal health information that is not obtained from a covered entity that is self-disclosed by research participants, and that is kept only in the researcher's records is not subject to HIPAA but is regulated by other human subjects protection regulations.

The Department of Health and Human Services' *National Standards to Protect the Privacy of Personal Health Information* are promulgated in the Health Insurance Portability and Accountability Act (HIPAA) of 1998, commonly referred to as the "Privacy Act." This Act specifies requirements for protection of individually identifiable health information (IIHI) or "protected health information" (PHI). PHI is individually identifiable health information (IIHI) such as name, address, social security number, email address, telephone number, etc., that is created, received or maintained by a Covered Entity (CE). A CE is a Health Care Provider that performs one of the standard electronic transactions identified in the HIPAA Privacy Rule; a Health Plan; or a Health Care Clearinghouse. Virtually all doctors, hospitals, and other health care facilities are Covered Entities.

A. Definitions

For the purposes of this discussion, it is important to understand certain definitions within the context of HIPAA:

1. Covered Entity

Covered entities are health care providers (*if they transmit any information in an electronic form in connection with a transaction for which HHS has adopted a standard*), health plans, health care clearinghouses, and their business associates.

2. Hybrid Entity

Georgia Tech is a hybrid entity, with only portions of the Institute subject to HIPAA. As a hybrid entity, any individually identifiable health information maintained by other components of the

university (i.e., outside of the health care component), such as a law enforcement unit, or a research department, would not be subject to the HIPAA Privacy Rule, notwithstanding that these components of the institution might maintain records that are not “education records” or treatment records under FERPA.

3. Authorization (Consent)

(Patient) authorization is the HIPAA equivalent of consent to use and disclose (patient) data.

4. Protected Health Information (PHI)

Protected health information includes all *individually identifiable* health information transmitted or maintained by an organization covered by the HIPAA regulations (a “covered entity”), regardless of form. Specifically, if it is Individually Identifiable Health Information (IIHI) that is:

- created or received by a health care provider, health plan, employer, or health care clearinghouse; **AND**
- personal health information that relates to:
 - the past, present, or future physical or mental condition,
 - the past, present, or future provision of care to an individual, or
 - the past, present or future payment for provision of health care to an individual, and
 - identifies the individual (or there is a reasonable basis to believe that the information can be used to identify the individual).

Health-related information is PHI if:

- The researcher obtains the information from a healthcare provider, health plan, health clearinghouse, business associate, or employer (other than records solely relating to employment status;

OR

- The records were created by a healthcare provider, health plan, health clearinghouse, or employer, AND the researcher obtains the records from an intermediate source which is not a school or employer record related solely to employment status;

OR

- The researcher obtains the records directly from the study subject in the course of providing treatment to him.

Health-related information is not considered PHI if the researcher obtains it from:

- Student records maintained by a school;

OR

- Employee records maintained by the employer for employment status;

OR

- The research subject directly, if the research does not involve treatment.

B. What Research Is Subject to the HIPAA Regulations?

Any research conducted under the auspices of Georgia Tech that creates, uses, or discloses protected health information obtained from a covered entity is subject to the Health Insurance Portability and Accountability Act (HIPAA).

C. Types of Health Information

There are three categories of health information. The requirements for use are different for each.

1. Individually Identifiable Health Information (IIHI)

IIHI includes any subset of health information, including demographic information collected from an individual, that:

- Identifies the individual (or there is a reasonable basis to believe that the information can be used to identify the individual.)
- The general rule is that an authorization signed by the research subject is required for the disclosure of individually identifiable health information. An IRB may waive this requirement.

2. De-Identified Data Sets

Health information is considered de-identified when it does not identify an individual and the covered entity has no reasonable basis to believe that the information can be used to identify an individual. Information is considered de-identified if 18 identifiers are removed from the health information and if the remaining health information could not be used alone, or in combination, to identify a subject of the information. An IRB may waive authorization for the use of de-identified data.

The 18 identifiers that may not be included in de-identified data sets are:

1. Names;
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the

initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census:

- The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
 - The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
 4. Phone numbers;
 5. Fax numbers;
 6. Electronic mail addresses;
 7. Social Security numbers;
 8. Medical record numbers;
 9. Health plan beneficiary numbers;
 10. Account numbers;
 11. Certificate/license numbers;
 12. Vehicle identifiers and serial numbers, including license plate numbers;
 13. Device identifiers and serial numbers;
 14. Web Universal Resource Locators (URLs);
 15. Internet Protocol (IP) address numbers;
 16. Biometric identifiers, including finger and voice prints;
 17. Full face photographic images and any comparable images; and
 18. Any other unique identifying number, characteristic, or code (This does not refer to the unique code assigned by the investigator to code the data).

3. Limited Data Sets

A *limited data set* is information disclosed by a covered entity to a researcher who has no relationship with the individual whose information is being disclosed. The covered entity is permitted to disclose PHI, with direct identifiers removed, *subject to obtaining a data use agreement from the researcher receiving the limited data set*. The PHI in a limited data set may not be used to contact subjects. The IRB may waive authorization for use of limited data sets in research.

Direct identifiers that must be removed from the information for a limited data set are:

1. Name,
2. Address information (other than city, State, and zip code),
3. Telephone and fax numbers,
4. E-mail address,
5. Social Security number,
6. Certificate/license number,
7. Vehicle identifiers and serial numbers,
8. URLs and IP addresses,
9. Full face photos and other comparable images,
10. Medical record numbers, health plan beneficiary numbers, and other account numbers,
11. device identifiers and serial numbers,

12. biometric identifiers including finger and voice prints.

Identifiers that are allowed in the limited data set are:

1. Admission, discharge and service dates,
2. Birth date,
3. Date of death,
4. Age (including age 90 or over),
5. Geographical subdivisions such as state, county, city, precinct and five digit zip code.

D. Authorization (Consent) Requirements

HIPAA regulations use the term “authorization” to describe the process through which a patient consents for researchers to access protected health information. Blanket authorizations for research to be conducted in the future are not permitted. Each new use requires a specific authorization. The authorization for disclosure and use of protected health information may be combined with the consent form that a research subject signs before agreeing to be in a study. It may also be a separate form. In either case, the information must include:

1. Elements of Required Authorization

- A description of the information to be used for research purposes;
- Who may use or disclose the information
- Who may receive the information
- Purpose of the use or disclosure
- Expiration date of authorization
- How long the data will be retained with identifiers
- Individual’s signature and date
- Right to revoke authorization
- Right to refuse to sign authorization (if this happens, the individual may be excluded from the research and any treatment associated with the research)
- If relevant, that the research subject’s access rights are to be suspended *while the clinical trial is in progress*, and that the right to access PHI will be reinstated at the conclusion of the clinical trial.
- That information disclosed to another entity in accord with an authorization may no longer be protected by the rule.

2. Waiver of Authorization for Research

The Institutional Review Board uses the following criteria in approving requests for a waiver of authorization for research:

- The use or disclosure of protected health information must involve no more than minimal risk to the privacy, safety, and welfare of the individual;
- The research could not practicably be conducted without the waiver or alteration; and
- The research could not practicably be conducted without access to the protected health information.

The Institutional Review Board must also consider if the researcher has provided:

- an adequate plan to protect the identifiers from improper use or disclosure;
- an adequate plan to destroy the identifiers at the earliest opportunity, unless retention of identifiers is required by law or is justified by research or health issues; and
- adequate written assurance that the PHI will not be used or disclosed to a third party except as required by law or permitted by an authorization signed by the research subject.

E. Information Needed for Review

Detailed information is needed about the types of information investigators will use in their research, how it will be used, who will have access to it, and when it will be destroyed. Specifically, researchers should address:

- What risks are posed by the use of the data and how have they been minimized?
- What is the justification for access to the data and why are they necessary to conduct the research?
- What plan does the researcher have to protect identifiers from improper use or disclosure?
- What is the researcher's plan to destroy the identifiers? If it is not possible to destroy the identifiers, what is the health, legal, or scientific justification?
- Has the researcher provided adequate written assurance that the PHI will not be used or disclosed to a third party except as required by law or permitted by an authorization signed by the research subject?

Researchers requesting waivers of authorization will need to explain that the use or disclosure poses no more than minimal risk to the subject; that the research could not practicably be conducted without the waiver; and that the research could not practicably be conducted without access to the protected health information. The researcher must explain:

- how the use of PHI involves no more than minimal risk to individuals

- why such a waiver will not adversely affect privacy rights or welfare of individuals in the study
- why the study could not practicably be conducted without a waiver
- why it is necessary to access and use protected health information to conduct this research
- how the risks to privacy posed by use of PHI in this research are reasonable in relation to the anticipated benefits
- the plan to protect identifiers from re-disclosure
- the plan to destroy identifiers. Provide a date by which this will take place. If identifiers must be retained, provide the reason (scientific, health, or other) why this is necessary.
- and confirm that the PHI will not be reused or disclosed to anyone else.

F. Human Subjects' Rights

1. Right to an Accounting

When a research subject signs an authorization to disclose PHI, the covered entity is not required to account for the authorized disclosure. An accounting is not required when the disclosed PHI was contained in a limited data set or is released to the researcher as de-identified data. However, an accounting is required for research disclosures of identifiable information obtained under a waiver or exception of authorization. Research subjects may request an accounting of disclosures going back for up to six years.

2. Right to Revoke Authorization

A research subject has the right to revoke his or her authorization unless the researcher has already acted in reliance on the original authorization. Under the authorization revocation provision, covered entities may continue to use or disclose PHI collected prior to the revocation as necessary to maintain the integrity of the research study. Examples of permitted disclosures include submissions of marketing applications to the FDA, reporting of adverse events, accounting of the subject's withdrawal from the study and investigation of scientific misconduct.

G. Subject Recruitment

1. Recruitment is Subject to the General Authorization Requirements

The Privacy Rule classifies recruitment as "research" rather than as health care operations or marketing. Because development or use of research databases falls within the definition of "research," a covered entity may disclose PHI in a database to sponsors for subject recruitment only after an authorization from the research subject or a waiver from the Institutional Review Board has been obtained.

2. Requirements to Disclose PHI Contained in a Limited Data Set or as De-Identified Data

It is easier to create databases of potential subjects' limited data sets to verify feasibility to conduct a clinical trial or to perform epidemiological research.

3. Limitations on Use of PHI in a Limited Data Set for Subject Recruitment

The PHI may not be used to contact subjects, and, because telephone numbers, internet provider addresses, and email addresses are not part of a limited data set, this information may not be collected by researchers from prospective subjects.

4. Recruiting Subjects Identified using their PHI

When researchers want to approach potential subjects to participate in a study who they have identified using PHI under a waiver of authorization, they must use an approach method that has been approved in advance by the IRB. Examples include using an intermediary such as the patient's primary care provider or a member of the medical staff actually caring for that patient, or sending the potential subject a letter signed by the patient's provider.

H. Requirements for Security of Protected Health Information under the Health Insurance Portability and Accountability Act (HIPAA)

All investigators performing human subject research that involves access to Protected Health Information (PHI) are required to comply with both the Privacy Rule and Security Rule of the Health Insurance Portability and Accountability Act (HIPAA).

The Office of Research Integrity Assurance and the Office of Information Technology (OIT) have partnered to ensure that researchers utilizing PHI are able to adequately safeguard those data. All researchers needing access to PHI shall complete the CITI HIPAA Privacy Rule training beforehand. Therefore, investigators who create, use or otherwise obtain individually identifiable health information are asked to:

1. Complete the HIPAA Privacy Rule training module at <https://oria.gatech.edu/regulatory-affairs/required-training>, REQUIRED TRAINING, and
2. Undergo a data security assessment conducted by the Office of Information Technology. (The Office of Research Integrity Assurance will inform OIT when such protocols are submitted; OIT will contact investigators directly to schedule assessment).

Only those computer terminals conforming to the Institute's HIPAA Rule Security Standards may be used for the creation, receipt, or maintenance of PHI. See also Appendix 2 of these *Policies & Procedures*, "Data Storage Guidelines."

With these provisions in mind, the Georgia Tech IRB requires that investigators who create, use or otherwise obtain PHI provide more detailed information about data storage, security, planned re-disclosure, and destruction; and provide more information to research subjects in the consent and authorization process about their PHI will be used.

It is a violation of this policy for any person performing work with PHI for Georgia Tech as an employee or independent contractor to fail to comply with any Privacy and/or Security Rule obligation for which they are responsible, regardless of whether such failure is intentional or not.

1. HITECH Act of 2009

On April 17, 2009, the Department of Health and Human Services (HHS) issued guidance specifying the technologies and methodologies that render protected health information unusable, unreadable, or indecipherable to unauthorized individuals, as required by the Health Information Technology for Economic and Clinical Health (HITECH) Act passed as part of the American Recovery and Reinvestment Act of 2009 (ARRA). This guidance was developed through a joint effort by the Office of Civil Rights, the Office of the National Coordinator for Health Information Technology, and the Centers for Medicare and Medicaid Services.

There are two breach notification regulations, one issued by HHS for covered entities and their business associates under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Sec. 13402 of HITECH), and the other issued by the Federal Trade Commission (FTC) for vendors of personal health records and other non-HIPAA covered entities (Sec. 13407 of HITECH).

2. Strengthened Enforcement Measures

Perhaps the most significant feature of the HITECH Act is the strengthening of HIPAA enforcement measures. Whereas the Office of Civil Rights (OCR) and the Department of Justice were the only HIPAA enforcement authorities previously, the Act authorizes state Attorneys General to enforce HIPAA violations in federal court. Should the Department of Justice not pursue criminal penalties for a violation that constitutes criminal behavior, the Office of Civil Rights is now authorized to pursue civil penalties for the same violation.

The Act includes new civil and criminal penalties for employees, with monetary fines being returned to OCR for future enforcement purposes and, eventually, to compensate victims. Civil monetary penalties for willful neglect violations were previously maxed at \$25,000; the Act tiers civil monetary penalties with a maximum of \$1.5 million.

**XV. Eligibility for the Title of
Principal Investigator on
Protocols**

Reviewed: July 2022

A. Eligibility for Title of Principal Investigator on Protocols

The term “Principal Investigator” refers to the single individual who shall have full and final responsibility for the conduct of a protocol (research study) involving human subjects. For IRB and Regulatory Affairs purposes, the title of Principal Investigator (PI) or co-Principal Investigator (co-PI) will be allowed when the individual is a current member of the Georgia Tech academic or research faculty as defined in the faculty handbook, or when the individual satisfies one of the exceptions specified below. Clinical investigators, regardless of their role(s) in the study, shall hold the appropriate current medical and/or state/federal licenses.

Academic faculty designations include varying levels of professor, professor of the practice, academic professional, archivist, librarian, lecturer and senior lecturer, and instructor. Also included in this category are the president, provost, vice provosts, executive vice president for research, executive vice president for administration and finance, college deans, dean of the libraries, dean of students, school chairs, and the registrar.

Research faculty include varying levels of regents researcher, research associate, research engineer, research scientist, research technologist, and extension professional. Others included are the president, provost, executive vice president for research, executive vice president for administration and finance, and director – research (as the term is used for GTRI lab directors).

Retirees: If the proposed PI or co-PI is retired and working on an hourly-as-needed basis, there must be at least one School, Laboratory, or Department willing to provide the necessary administrative commitment to permit the protocol to be carried out. This arrangement must be documented in writing in the protocol.

Postdoctoral Fellows may serve as PI or co-PI if the relevant department head signs off on the protocol. This includes Brittain Fellows.

Adjunct faculty may not serve as PI or co-PI on an IRB protocol *unless they are also eligible to be a PI as described above*. They may hold the title of co-investigator if they sign a Visiting Scholar Agreement. (Some personnel are faculty in the Georgia Tech Research Institute and also adjunct in an academic unit; some personnel may be faculty in one academic unit and adjuncts in another).

Affiliates may not be named as PI or co-PI.

Non-employees are not generally eligible to serve as a PI or co-PI on protocols. Requests for exceptions for a non-employee to serve as PI or co-PI on a specific protocol for a limited time may be directed to the Executive Vice President for Research. This exception is generally appropriate for newly hired faculty in transition from another institution and enables research to continue with minimal interruption.

Occasionally, an individual who is not otherwise eligible for the title of PI or co-PI may receive an exception letter from the Executive Vice President for Research, as described in item B., below. Some students may also qualify under C. 1 or 2, below.

B. Additional Principal Investigator Credentials Required by FDA

For studies subject to the Food & Drug Administration regulations, investigator credentials including, if applicable, license to practice medicine, must be verified by the Institutional Review before IRB approval can be given. Companies and medical practices must also provide copies of their business licenses.

If conducting drug/pharmaceutical studies, investigators must also review, date, and sign the *FDA Guidance on Investigator Responsibilities*. (See Appendix 21, *FDA Guidance for Sponsors, Clinical Investigators, and IRBs Regarding FDA Form 1572*) and the Frequently Asked Questions on the FDA Form 1572 (See Appendix 22, *FDA Guidance for Sponsors, Clinical Investigators, and IRBs Regarding FDA Form 1572*).

C. Exceptions Requiring Approval by the Executive Vice President for Research

Exceptions to the general eligibility requirements for designation as Principal Investigator will be considered upon submission of a written request to the Executive Vice President for Research. The request should justify why the individual should be designated as the Principal Investigator and must be signed by the appropriate departmental representative (Chair, Director, or Department Head). A copy of the approved exception, signed by the Executive

Vice President for Research and the requesting department's head, must be provided to the Office of Research Integrity Assurance before a protocol will be approved.

D. Eligibility Exceptions for Graduate and Undergraduate Students as Principal Investigators

Usually, graduate and undergraduate students are named as Co-Investigators, as this title designates key personnel but does not have the oversight responsibilities of a Principal Investigator. Exceptions to allow graduate and undergraduate students to use the title of Principal Investigator on an IRB protocol are described below.

1. Exception for Georgia Tech Students Receiving Stipends and Tuition in Support of Their Work on Emory Protocols

In those few cases where the Principal Investigator is a faculty member at Emory University, AND no Georgia Tech faculty member has any involvement in the project, AND the funding (if any) is awarded to Emory University with a subcontract to Georgia Tech solely for the student's stipend and tuition, AND a Georgia Tech student is being mentored and supervised by the Emory University Principal Investigator, the Georgia Tech student will be named Principal Investigator (PI) for Georgia Tech's tracking purposes.

In addition to completing the required training modules in human research protections, the student must be named in the approved Emory protocol, AND the only funding from Emory University to Georgia Tech must be for the student's stipend and tuition.

The Georgia Tech student PI must submit to the Georgia Tech Office of Research Integrity Assurance:

- A copy of the approved Emory IRB protocol;
- A copy of the Emory IRB letter of approval;
- The protocol title must start with the word EMORY; and
- The funding source must be clearly identified.

The Student PI must meet with a Research Associate in the Georgia Tech Office of Research Integrity Assurance for a brief overview of PI responsibilities before a letter of approval will be issued to the student from the Georgia Tech IRB.

2. Exception for Georgia Tech Students Receiving Fellowships Supporting Their Work on Emory Protocols

In those few cases where the Principal Investigator is a faculty member at Emory University, AND no Georgia Tech faculty member has any involvement in the project, AND a Georgia Tech student is being mentored and supervised by the Emory University Principal Investigator, AND the funding awarded to Georgia Tech is solely for the student's fellowship, the Georgia Tech student can be named Principal Investigator (PI) for Georgia Tech's tracking purposes.

In addition to completing the required training modules in human research protections, the student must be named in the approved Emory protocol, AND the only funding from Emory University to Georgia Tech must be for the student's fellowship.

The Georgia Tech student PI must submit to the Georgia Tech Office of Research Integrity Assurance:

- A copy of the approved Emory IRB protocol;
- A copy of the Emory IRB letter of approval;
- The protocol title must start with the word EMORY; and
- The funding source must be clearly identified

The Student PI must meet with a Research Associate in the Georgia Tech Office of Research Integrity Assurance for a brief overview of PI responsibilities before a letter of approval will be issued to the student from the Georgia Tech IRB.

E. Circumstances That Render Researcher Ineligible to Hold Role of Principal Investigator, Co-Principal Investigator, or Investigator

At initial and continuing review, the Institutional Review Board shall consider whether *any* study personnel fits any condition of the following:

- If involved in an investigation or other research that was terminated, an explanation of the circumstances leading to termination must be provided. (21 CFR 812.43(c)(3))
- Has been debarred.
- Has a restriction, limitation, judgment on his license or its status (if a license is applicable to that person).
- Has any prior regulatory inspection history that resulted in an official written citation, such as an FDA warning letter.

F. Definitions

1. Principal Investigator

This title identifies the individual responsible for the conduct of the study. This responsibility includes the conduct of the study, all

administrative aspects, and the study's adherence to relevant policies and regulations (institutional, state and federal).

2. Co-Principal Investigator

This designation refers to individuals who share the responsibility for the study with the Principal Investigator and therefore requires the same qualifications as for PI.

3. Co-Investigator

This title designates key personnel for a project, but without the oversight responsibility of a Principal Investigator. Individuals do not need to meet the qualifications of PI under this policy to be named a Co-Investigator, but should be key personnel on the project. For example, a Master's or PhD student submitting his or her dissertation for IRB approval may be listed as the Co-investigator. The thesis or dissertation chair/advisor should be listed as the PI on the IRB application. An undergraduate working on a senior thesis or other class research project should list himself as the Co-investigator. The faculty member who is advising the student on the research should be listed as the PI for IRB purposes.

In addition, faculty members may be listed as Co-Investigators if their role on the study is not that of PI or Co-PI.

XVI. Research in International Settings

Reviewed: July 2022

If a study team is conducting research in an international setting, the study team must comply with local laws for where the study is taking place. Additionally, the study team must confirm with the country's office that regulates medical products to ensure that all laws and regulations are being followed. Documentation from the country's office that regulates medical products may be requested by the Georgia Institute of Technology's Regulatory Affairs and Clinical Trials office.

FDA Export Certificates

Firms exporting products from the United States are often asked by foreign customers or foreign governments to supply a "certificate" for products regulated by the Food and Drug Administration (FDA). A certificate is a document prepared by FDA containing information about a product's regulatory or marketing status.

Export Control

If you are receiving or transporting data, FDA regulated products, and/or samples internationally, you may need Export Control review. Furthermore, if you are collaborating with foreign investigators, you may also need Export Control review. Please contact Export Control for more information.

**XVII. Other Agreements, Issues,
and Reviews for your
Consideration**

Reviewed: July 2022

When conducting FDA regulated research with animals, rDNA, bio-specimen, and/or conducting off-campus research or research with data and/or materials from external institutions, specific agreements and reviews may be needed prior to the research taking place. A list of Georgia Tech regulatory bodies, common issues, and agreements are listed below along with information regarding each item. Please note that other issues and agreements that are not listed below may be needed due to the specifics of your research.

A. Biological Material Safeguards Committee (BSMC)

If you are receiving, storing, and/or using biological samples for the purposes to conduct research on an FDA regulated product, BSMC approval may be needed. An example would be establishing a tissue repository to create an assay for a specific disease. The receiving and storing of the tissue may require approval from BSMC before any tissues are received and stored. Please contact BSMC for further information.

B. Business Associate Agreement (BAA)

A “business associate” is a person or entity, other than a member of the workforce of a covered entity, who performs functions or activities on behalf of, or provides certain services to, a covered entity that involve access by the business associate to protected health information. A “business associate” also is a subcontractor that creates, receives, maintains, or transmits protected health information on behalf of another business associate. The HIPAA Rules generally require that covered entities and business associates enter into contracts with their business associates to ensure that the business associates will appropriately safeguard protected health information. Please contact the Office of Legal Affairs for more information.

C. Clinical Trial Agreements (CTA)

When either supporting a clinical trial taking place at another institution or when another institution is supporting a Georgia Tech clinical trial, a CTA may be needed to legally establish the relationship between the sponsor

(organization providing the study drug or device, the financial support and/or proprietary information) and the institution that may be providing data and/or results, publication, input into further intellectual property. An example would be when a Georgia Tech investigator is conducting data analysis and is involved in the publication process with a clinical trial taking place at one of the local hospitals. Please contact the Office of Regulatory Affairs for more information.

D. Data Use Agreement (DUA)

A Data Use Agreement specifies the terms and conditions under which a Georgia Tech researcher receives a Limited Data Set from a Covered Entity. Please contact the Office of Legal Affairs for more information.

E. Institutional Animal Care and Use Committee (IACUC)

If you are conducting FDA regulated research that involve vertebrate animals, you may need IACUC approval. An example of this would be conducting Good Laboratory Practice (GLP) research on animals prior to conducting the research with humans. Prior to the use of these animals, IACUC approval is needed. Please contact IACUC for further information.

F. Institutional Biosafety Committee (IBC)

If you are conducting FDA regulated research with recombinant DNA and synthetic nucleic acid molecules (rDNA) at Georgia Tech, you may need IBC approval. An example would be conducting animal experiments while using rDNA to intentionally alter traits within the animal. Please contact IBC for further information.

G. Insurance

In cases where FDA regulated products are being manufactured and used at different organizations, issues with insurance may arise. More specifically, if an external organization manufactured a device for Georgia Tech investigators, and the device was to be used either in research or for therapeutic use, the two entities will need to determine who is liable if any issues arise. For these scenarios, please contact the Office of Industry Engagement.

H. Licensing

Licensing is a way for Georgia Tech technology and innovations to be used in the marketplace. In terms of FDA regulated products, licensing can allow a Georgia Tech researcher to develop an investigational medical device. The GT researcher can then license the device to either another institution or sponsor

so they can use the technology in a clinical trial, in which GT is not involved in. Please contact the Office of Industry Engagement for more information.

I. Loan Equipment Agreements

The State of Georgia General Statutes requires the Institute to be accountable for all equipment under its control. The purpose of agreement is to formalize our understandings regarding the equipment by the University, and to set forth our mutual understandings regarding the care, custody and disposition of such equipment. Please contact the Office of Legal Affairs for more information.

J. Material Transfer Agreement (MTA)

A material transfer agreement (MTA) is a contract between the Georgia Tech Research Corporation and another party that governs the transfer of tangible research materials. These materials include, but are not limited to, chemicals and biological materials such as cell lines, vectors, and plasmids. An MTA defines the rights of the provider and the recipient with respect to the use of the exchanged material and any derivatives. It also details how to manage any intellectual property. Please contact the Office of Legal Affairs for more information.

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

**XVIII. Non-Georgia Tech Personnel
(including Visiting Scholars and
Minors) Participating in Conduct of
Protocols at Georgia Tech**

Reviewed: July 2022

Georgia Tech celebrates and fosters collaborative relationships with non-Georgia Tech researchers and scientists who visit the Institute and who may wish to participate as researchers in projects at Georgia Tech. In order to ensure appropriate protections for those visitors and for Georgia Tech faculty and staff, this policy has been developed:

Any visiting non-Georgia Tech personnel wishing to participate as a researcher on a study involving human subjects must complete a VISITING SCHOLAR AGREEMENT with the Georgia Tech Office of Legal Affairs, and must either be named in the original protocol application or be added by amendment to an existing protocol prior to participation in the protocol.

The Visiting Scholar's current CV or completed credentials form must be submitted to the Office of Research Integrity Assurance, and the Visiting Scholar must either complete the GT-required CITI training modules or present documentation of completion of another acceptable course. Upon approval by the IRB, such Visiting Scholars may serve as co-investigators working with Georgia Tech Principal Investigators who are responsible for conducting the research and ensuring compliance with the approved protocol.

The Georgia Institute of Technology has set forth specific eligibility requirements for the title of Principal Investigator (PI). These requirements apply not only in regard to IRB protocols, but also for protocols involving vertebrate animals or rDNA, and for serving as a PI on a sponsored project.

A. Participation of Minors as Employees or Volunteers in Laboratory and Other Activities Related to Human Subjects Research

Occasionally, minors, ages 16 or 17, will work in laboratories and other research environments at Georgia Tech. Some minors are employed as Tech Temps, while others are volunteers. These scholarly activities are enriching and often cement minors' interest in pursuing higher education in science, technology, engineering and mathematics (STEM) fields.

Georgia Tech's Office of Human Resources can provide guidance to departments hiring minors, including requirements of the Board of Regents (BOR) of the University System of Georgia that must be followed. The BOR requirements are set forth in their Human Resources Administrative Practice Manual which is posted online at <https://www.usg.edu/hr/manual>. Some of the requirements are:

- Each institution may allow departments to hire persons age sixteen and seventeen into temporary positions during recognized school breaks under certain conditions.
- If the minor is to work or volunteer in a laboratory setting or other hazardous area, the Supervising Faculty Member and/or Mentor must contact Georgia Tech's Office of Environmental Health and Safety and complete an "*Application for Authorization of a Minor (16 or 17 years of age) to Work or Volunteer in a Laboratory or other Hazardous Area.*" This authorization must occur prior to the start date.
- The parent/legal guardian of the minor must also complete the "*Consent for Minor's Presence in Laboratory*" form and return it to Georgia Tech's Office of Environmental Health and Safety. Execution of this form is important, and it must be accomplished prior to the minor beginning to work or volunteer.
- Minors who are volunteers must provide evidence of personal health insurance as the Minor is responsible for his or her own medical care and all associated costs.
 - The department hosting the volunteer should retain the insurance information and all other necessary documentation for hosting the volunteer. Releases should be obtained and/or Risk Management should confirm that there is a recognized volunteer program for insurance coverage.
 - The department must also ensure compliance with the Georgia Tech Child Abuse Prevention policy, which is posted online at <http://www.policylibrary.gatech.edu/mandatory-reporting-child-abuse-policy>.
- The BOR requires that the supervising faculty member or mentor shall have constant line-of-sight supervision of the Minor at all times *while in the laboratory*.

XIX. Adverse Events and Unanticipated Problems

Revised: July 2022

Federal regulations at [§21CFR56.108\(b\)\(1\)](#) and at [§45CFR46.103](#) require the IRB to follow written procedures for ensuring prompt reporting to the IRB of any unanticipated problems involving risk to human subjects or others.

Guidance from the Office for Human Research Participants (OHRP) states that, before research is approved and the first subject enrolled, the investigator(s) and the IRB should give appropriate consideration to the spectrum of adverse events that might occur in subjects. In particular, in order to make the determinations required for approval of research under HHS regulations at [§45CFR46.111](#), the IRB needs to receive and review sufficient information regarding the risk profile of the proposed research study, including the type, probability, and expected level of severity of the adverse events that may be caused by the procedures involved in the research. The investigator also should describe how the risks of the research will be minimized.

A. Adverse Events

The FDA defines an adverse event as *any undesirable experience associated with the use of a medical product in a patient*. The HHS regulations at [§45CFR46](#) do not define or use the term *adverse event*, nor is there a common definition of this term across government and non-government entities. The Office for Human Research Protections (OHRP) utilizes this definition: *An adverse event is “Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).”*

Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, but they can also occur in social and behavioral research.

An adverse event may be both serious and unanticipated.

1. Serious Adverse Events

A *serious adverse event* is one that is fatal, life-threatening, persistent, significantly disabling or incapacitating, requires inpatient hospitalization or prolongation of hospitalization, results in congenital anomaly or defect, and/or that is a significant medical incident. (A significant medical incident is considered a serious, study-related adverse event because it may jeopardize the subject's health and may require medical or surgical intervention to prevent a poor outcome.)

The FDA requires that serious events be reported when the patient outcome is:

- **Death:** Report if the patient's death is suspected as being a direct outcome of the adverse event.
- **Life-Threatening:** Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. *Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing.*
- **Hospitalization (initial or prolonged):** Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event. *Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing or prolonging hospitalization.*
- **Disability:** Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life. *Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity; peripheral neuropathy.*
- **Congenital Anomaly:** Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child. *Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.*
- **Requires Intervention to Prevent Permanent Impairment or Damage:** Report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient. *Examples: Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage; burns from radiation equipment requiring drug therapy; breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.*

2. Unanticipated Adverse Events

An *unanticipated adverse event* is one that results from a study intervention and was not expected or anticipated. Expected adverse events that occur with greater frequency or severity than expected may be characterized as unanticipated adverse events.

3. Unanticipated Adverse Device Effects (UADEs)

The Food & Drug Administration (FDA) investigational device exemption (IDE) regulations define an *unanticipated adverse device effect (UADE)* as “*any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.*” (§21CFR812.3(s))

4. When Adverse Events Must Be Reported

Investigators are required to *report to the Institutional Review Board within ten days of its occurrence* any serious problem, serious adverse event, or other outcome that occurs more frequently or with greater severity than anticipated. Further, if any event(s) cause the suspension, whether temporary or permanent, of a research study involving human subjects, the IRB must be informed within ten days. Such reports to the IRB must describe the adverse events’ relevance and significance to the study and whether there is a change in the risk of participation.

When the GT PI is managing a study site on an NIH-supported multi-center clinical trial, in lieu of receiving individual adverse event reports from each of the clinical sites, the GT IRB should receive from the investigator a written summary report whenever a data safety monitoring board (DSMB) review has taken place.

Adverse events that are of minimal risk and anticipated (such as skin irritation from tape/sensors) may be reported at the next continuing review.

Adverse events are to be reported to the GT IRB via IRBWISE. Very serious and unanticipated events may be immediately reported by telephone to the Office of Research Integrity Assurance at 404 / 894-6942 or 404 / 894-6949. Investigators are responsible for the accurate documentation, investigation and follow-up of all possible study-related adverse events.

a. PI-Initiated Studies

When the investigator is the study sponsor—that is, when he is the holder of the Investigational New Drug (IND) or Investigational Device Exemption (IDE)—he is responsible for reporting serious adverse events directly to the IRB and to the Food and Drug Administration (FDA). FDA requires use of the Form #3500a (Mandatory Medwatch Form).

b. Industry Sponsored Studies

When the study is industry-sponsored, the PI will also be required to report serious and unanticipated adverse events and problems to the sponsor, as well as to the GT IRB. This form may also be used to voluntarily report serious adverse events, potential and actual medical product errors, and product quality problems associated with the use of FDA-regulated drugs, biologics, devices and dietary supplements. Study sponsors may have different reporting processes.

Unanticipated Adverse Device Effects (UADEs) must be reported to the IRB and the sponsor within 10 working days after the investigator first learns of the effect (§812.150(a)(1)). Sponsors must immediately evaluate reports of an UADE and report the results to the FDA, all reviewing IRBs, and participating investigators within 10 working days after first receiving notice of the effect (§812.46(b), 812.150(b)(1)).

B. Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

An unanticipated problem is an event that was not anticipated or foreseen, involves risk to subjects or others and, in the judgment of the investigator, was related to or caused by the research activity. The loss of a laptop computer containing confidential information about subjects is an example of an unanticipated problem. In such cases, while subjects may not be physically harmed, the potential breach of confidentiality may cause them anxiety or embarrassment.

1. Requirement for Investigators to Report Unanticipated Problems

Serious unanticipated problems must be reported to the Office of Research Integrity Assurance by the Principal Investigator within ten working days of their occurrence. Very serious and unanticipated events may be immediately reported by telephone to the Office of Research

Integrity Assurance at 404 / 385-2175 or 404 / 894-6942. Other unanticipated problems should be reported within thirty days. Any protocol deviation to mitigate immediate risk or potential harm should also be reported. These reports may be submitted online via IRBWISE.

Such reports must include a complete description of what happened, when and where the event took place, and any resulting harm or injury to a subject or others. Principal Investigators must report to the Office of Research Integrity Assurance any injury to a human subject; unanticipated problems; new information that affects risk/benefit, and any evidence of research misconduct involving risks to research subjects. Reports of unanticipated problems should explain why the event represents a problem for the study and why it was unanticipated.

2. Requirement for Investigators to Monitor Problems

The Principal Investigator must monitor anticipated problems, subject complaints and any other issues that do not constitute an unanticipated problem requiring reporting to the IRB. These events should be recorded in a log maintained by the PI or research staff. The PI should consider whether such problems, complaints, or issues necessitate modification of the consent document or other protocol amendment.

C. Institutional Review Board Response to Reports of Adverse Events and Unanticipated Problems

Serious adverse events that occur on-site will be reviewed by the full committee at a convened meeting. Those occurring at another center conducting the study (i.e., in the case of multi-center studies) will be reviewed by the IRB in a timely manner.

The IRB may suspend or terminate approval of research at its site when there is unexpected serious harm to subjects. Such action shall be with the majority vote of IRB members at a convened meeting with a quorum. The Institutional Official will be immediately informed when the IRB makes such a determination. The Principal Investigator will also be immediately informed and will be provided a written statement of the action and the reasons for it. The IRB will also inform appropriate the Department or Agency head, the Office for Human Research Protections and the FDA, if an investigational new drug or device is involved. The IRB will communicate concerns to the Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), if any, and/or to the sponsor of the study if it believes that the safety of study participants is in jeopardy.

The IRB Chair and the Institutional Official shall each have independent authority to suspend a study immediately when, in their judgment, human

subjects are at risk of immediate harm. Such actions shall be reported to the IRB at the next convened meeting, when the Board will determine whether such suspended study may continue.

These actions and IRB deliberations shall be documented in the meeting minutes and be retained in accordance with records requirements.

D. Incidental Findings

Incidental findings are possible medical abnormalities that may have clinical implications and are observed in the course of research studies but are unrelated to the topic under study. Examples might include:

- A study involving fractionation of normal human blood suggests a potential infection;
- A baseline study of mental status indicates a psychiatric condition;
- A screening protocol for an exercise intervention identifies a cardiac insufficiency;
- A brain imaging study of depressed individuals reveals a potential structural abnormality (From Nature, Vol. 433. January, 2005, p. 185.).

No National Institutes of Health (NIH) policies/guidance specifically address incidental findings, however, NINDS, NIDA, NIBIB, NIMH, NIA and Stanford University sponsored a meeting in 2005 on “Detection and Disclosure of Incidental Finding in Neuroimaging Research.” See more information at http://www.ninds.nih.gov/news_and_events/proceedings/ifexecsummary.htm.

At this point, the NIH Office of Extramural Research (OER) suggests that investigators who propose studies that may result in incidental findings describe their plans for addressing incidental findings in the Human Subjects section of their applications as follows:

- how observed incidental findings will be handled by research staff, and
- how plans for handling incidental findings will be presented to potential participants during the informed consent process

More details are available at http://grants.nih.gov/grants/policy/hs/faqs_aps_hsp.htm#342.

The Georgia Tech IRB has written consent language, italicized below, that is required for MRI/fMRI studies conducted at the Joint Brain Imaging Center. Researchers may use this as a sample to develop similar language for other studies when appropriate.

“This MRI is done for research purposes only. The MRI scan being done is designed to answer research questions, not to medically examine your brain. The MRI scan is not a substitute for one a physician would order. It may not show

problems that would be picked up by a medical MRI scan. None of the researchers are medically qualified radiologists. However, if we see something unusual in your scan, we will inform you so that you can obtain a follow-up evaluation by your physician. Any follow-up evaluation or treatment that you seek will be at your own expense. Even if your physician rules out any problems, you may be unnecessarily worried if a problem is suspected.”

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

APPENDICES

Reviewed: July 2022

- APPENDIX 1: Investigator Agreement**
- APPENDIX 2: Data Storage Guidelines and Resources**
- APPENDIX 3: Additional Requirements Incorporated by Addendum to Federalwide Assurance for Research Involving Department of Defense (DOD)**
- APPENDIX 4: Scientific Review Template for DOD Protocols**
- APPENDIX 5: Nanotechnology Guidance, “Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology”**
- APPENDIX 6: FDA Guidance for Sponsors, Clinical Investigators, and IRBs Regarding FDA Form 1572**
 - A: Copy of Form 1572**
 - B: Investigator Responsibilities for Significant Risk Device Investigations**
- APPENDIX 7: Frequently Asked Questions, Statement of Investigator (Form FDA 1572)**
- APPENDIX 8: FDA Draft Guidance for Industry and FDA Administration Staff – Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies**
- APPENDIX 9: FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND**
- APPENDIX 10: Georgia Tech Regulatory Affairs Office ClinicalTrials.gov Database Initial Questions Document**

**APPENDIX 11: Georgia Tech Regulatory Affairs Office ClinicalTrials.gov
Database Interventional Questions Document**

**APPENDIX 12: Georgia Tech Regulatory Affairs Office ClinicalTrials.gov
Database Observational Questions Document**

Appendix 1: Investigator Agreement

Principal Investigators who propose to conduct a clinical study involving a medical device must complete an Investigator Agreement and include it with their protocol for IRB review.

GEORGIA INSTITUTE OF TECHNOLOGY INSTITUTIONAL REVIEW BOARD

INVESTIGATOR AGREEMENT FOR A CLINICAL INVESTIGATION OF THE

(Specify Investigational Device)

(Protocol Number and Study Title)

Relevant Definitions:

- **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.
- **Investigation** is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.
- **Investigator** is an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving a subject. In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team.
- **Sponsor-investigator** is an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an investigator *and* those of a sponsor.
- **Subject** is a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or who participates as a control. A subject may be in normal health or may have a medical condition or disease.

I AGREE AND/OR CERTIFY THAT:

1. I agree to participate as the Principal Investigator in *a clinical investigation of the investigational device specified above*. I have been provided links to the following Food and Drug Administration (FDA) regulations: 21 CFR Part 812, Investigational Device Exemptions; 21 CFR Part 50, Protection of Human Subjects; and 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

2. I will conduct the clinical investigation in accordance with this agreement; with all requirements of the investigational plan (protocol), Investigational Device Exemption (IDE) regulations, other applicable regulations of the FDA; with adherence to the principles of good clinical practices; and any conditions of approval imposed by the Georgia Institute of Technology Institutional Review Board (IRB), by any other IRB or Ethics Committee that reviews and approves this study, or by the FDA. I agree to abide by all of the investigator responsibilities enumerated at 21 CFR Part 812, Subpart E and Subpart G, including but not limited to the following:
 - a. I will obtain written approval from the Georgia Institute of Technology Institutional Review Board in advance of undertaking any activities with human subjects. If I am not also the sponsor-investigator of the corresponding IDE application, I will submit the certification of IRB approval and any conditions of this approval to the sponsor (sponsor-investigator).
 - c. I will supervise all testing of the *investigational device specified above* on human subjects and will allow only those individuals who are qualified by education, licensure, and/or the governance of the local medical board to perform these tests.
 - d. I will ensure that Informed Consent is obtained from each subject participating in this clinical investigation in accordance with the informed consent regulation found in 21 CFR Part 50, and that a signed copy of the informed consent shall be available to the sponsor (sponsor-investigator) and the sponsor's (sponsor-investigator's) designated monitor.
 - e. I will be responsible for accountability of the *investigational device specified above* at the study site and, if I am not also the sponsor-investigator of the corresponding IDE application, I will return all unused *investigational devices specified above* to the sponsor (sponsor-investigator) or otherwise follow the instructions of the sponsor (sponsor-investigator) for disposal of the unused devices.
 - f. I will ensure the accurate completion of protocol case report forms and, if I am not also the sponsor-investigator of the corresponding IDE application, I will submit completed protocol case report forms, progress reports, and a final report to the sponsor (sponsor-investigator) at the time frames specified in the Protocol and/or FDA regulations.
 - g. I will direct the retention of required records and documents related to the investigation.
3. I have the appropriate, relevant qualifications to conduct and to oversee the conduct of the investigation as documented by the following: (*Check applicable statement*)

_____ My relevant qualifications, including dates, location, extent, and type of experience, are listed in my most recent curriculum vitae (CV), which is attached to this Agreement and which will be maintained by the sponsor (sponsor-investigator) of the corresponding IDE application.

_____ My curriculum vitae (CV) does not reflect my relevant qualifications, therefore attached to this Agreement is a statement of my relevant experience (including dates, location(s), extent, and type of experience) which will be maintained by the sponsor (sponsor-investigator) of the corresponding IDE application.
4. There are no reasons to question my ability to oversee the appropriate conduct of this clinical investigation. (*Check applicable statement.*)

_____ Signature	_____ Date
_____ Name (please print or type)	
_____ Signature	_____ Date
_____ Name (please print or type)	
_____ Signature	_____ Date

Certification of Financial Interest of Investigators

Title of Study: _____

Principal Investigator: _____

Name of Investigational Drug/Device: _____

As an investigator who will be participating in the above-specified clinical study being conducted under a University-based (i.e., investigator-sponsored) or University-sponsored IND or IDE application, I certify that (*check the appropriate box for each statement*):

I do I do not Have an ownership interest, stock options, or other financial interest (i.e., *equity interest*) in the company (public or non-public) that owns the investigational drug or device being evaluated in the clinical study.

I do do not Have property or other financial interest (i.e., *proprietary interest*) in the investigational drug or device being evaluated in this clinical study; including, but not limited to, a patent or patent interest, trademark, copyright, licensing agreement, or any arrangement tied to a current or future right to receive royalties associated with the development or eventual commercialization of the drug or device.

I will I will not Receive payments from the company (i.e., other than the University) that owns the respective investigational drug or device during the term of the conduct of the clinical study; nor do I anticipate receiving payments from the company during a 1 year period following completion of the study. Applicable payments (i.e., *financial interest*) include, but are not limited to, grants to fund projects or research or compensation in the form of monetary payments, equipment, or retainers for consultation or honoraria.

If the response to any of the above statements is affirmative, submission of your approved Conflict of Interest Management Plan is required.

Name of Investigator (Printed or Typed)

Signature of Investigator

Date

Appendix 2: Data Storage Guidelines and Resources

The Office of Information Technology provides guidance on protecting and backing up sensitive data in electronic format is posted at:
<https://security.gatech.edu/information-security-procedures-and-standards>.

Researchers should work with the technical lead in their college to prevent unauthorized or inadvertent release of human subjects' individually identifiable health information, protected health information (PHI), and any other sensitive information. In some cases, unauthorized or inadvertent releases can result in enforcement actions by federal agencies.

In the event of a data breach, investigators should immediately contact the Office of Information Technology AND the Office of Research Integrity Assurance for assistance and guidance, particularly when the disclosure of data poses a significant risk for the subjects. OIT 's Information Security group will respond quickly to secure any breach in data security. The IRB will assist the investigator in determining when and whether it is necessary to inform subjects.

The Georgia Tech Library, through its DMPTool, offers assistance with data management plans. This web application, located at www.cdlib.dmp.edu, walks researchers step-by-step through the data management planning process. Sample NIH and NSF data management plans are available, as are links to guidelines for sharing and archiving data related to human subjects.

Scholarly Materials And Research @ Georgia Tech (SMARTech), located at <https://smartech.gatech.edu/>, is an institutional repository available to researchers whose funding agency or other organizations do not maintain a data archive or repository that will accept research data. Researchers intending to use SMARTech should include the following information in their data management plans for submission to the IRB: *“Any dissertation and any sharable research data related to this project will be deposited into SMARTech, or Scholarly Materials And Research @ Georgia Tech. SMARTech is a trusted digital repository that captures the intellectual output of the Institute in support of its teaching and research missions. Digital materials in the repository are available to Georgia Tech and the world. All Georgia Tech dissertations are published via this mechanism, which is searchable through internet search engines such as Google. The Library and SMARTech are committed to adhering to the best practices of the profession applying to digital preservation.”* For more assistance with creating data management plans or using the SMARTech repository, contact the Research Data Librarian at the Georgia Tech Library.

Appendix 3: Additional Requirements for Research Involving Department of Defense, Incorporated by Addenda to Federalwide Assurance

An Addendum to Georgia Tech's Federalwide Assurance incorporates the Department of Defense's (DoD) additional requirements for human subjects research involving the DoD. Human subjects research involves the DoD when any of the following apply:

- The research is conducted by or in part by the DoD.
 - Research involving human subjects that is performed by DoD personnel.
- The research is supported by the DoD.
 - Research involving human subjects for which the Department of Defense is providing at least some of the resources. Resources may include but are not limited to funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by a non-DoD institution.

A. Human Subjects Research as Defined by the DoD

Except as detailed in §32CFR219.104, this policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research (§32CFR219.101).

- Human Subject (§32CFR219.102)
 1. Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
 - i. Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.
 2. Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

3. Interaction includes communication or interpersonal contact between investigator and subject.
 4. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).
 5. Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
 6. An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.
- Research (§32CFR219.102)
 - Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research:
 1. Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
 2. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated

with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

B. Specific DoD Requirements

The DoD requirements, which comport with DoDI 3216.02 and include those that are component-specific, are described below. (These additional requirements do not apply when DoD personnel incidentally participate as subjects in research that is not supported by DoD).

1. EDUCATION

Investigators and all members of the research team must satisfy research ethics education initially and on a continuing basis [DoDI 3216.02].

• Air Force Research Laboratory (AFRL)

The Air Force Research Laboratory requires initial and recurrent training in the protections of human subjects for all personnel named in the protocol. Non-DoD personnel acting under a non-DoD Assurance are required to complete training prior to three years from the date of the previous training. Initial and recurrent training for investigators will consist of the designated AFRL modules on the Collaborative Institutional Training Initiative (CITI) web site. *The Air Force will accept Georgia Tech's regular CITI modules, in lieu of the Air Force modules, for undergraduate researchers. If substituted for the AF modules, the Georgia Tech CITI modules must also be completed every three years.* [AFRLI 40-402]

• Department of the Army

The US Army Medical Research & Materiel Command (AMRMC) *Guidelines for Investigators* state: "Before conducting human subjects research, the investigators and key study personnel must complete human research protection training in accordance with their institution's requirements. Principal and Co-Investigators must submit documentation of the most recent human research protection training to the HRPO as part of the submission package for the protocol. Training may also be requested for other research personnel with significant interaction with research volunteers. The HRPO requires that human research protection training be

successfully completed within the last three years. In addition, for all investigational drug and device protocols, successful completion of a course in the conduct of clinical research in accordance with Good Clinical Practices (GCP) is recommended for all investigators.” [United States Army Medical Research and Materiel Command (USAMRMC) Policy #2010-33, Requirements for Initial and Ongoing Education and Training in the Protection of Human Subjects in Research, dated 10 December]

The US Army Research Development & Engineering Command (ARDEC) requires that training be completed initially and every two years.

For sponsors other than USAMRMC and ARDEC, contact the Army program officer for specific information about specific education requirements.

- **Department of Navy (DON)**

DON requires initial and recurrent training by all investigators every three years. The DON will accept Georgia Tech’s human subjects research CITI training modules, in lieu of the DON modules. [SECNAVINST 3900.39E]

- **Office of the Secretary of Defense for Personnel and Readiness**

Initial and annual training is required for all investigators, per HA Policy 05-003.

The Georgia Tech IRBs will accept completion of any DOD-mandated CITI modules as sufficient and will not also require completion of the Ga Tech CITI modules. Personnel completing the DOD CITI modules will need to forward their CITI certificates to the Office of Research Integrity Assurance via email to irb@gtech.edu.

Georgia Tech requires completion of CITI refresher modules every three years. The Office of Research Integrity Assurance will assist those needing to meet an agency-imposed requirement for more frequent training.

2. SCIENTIFIC REVIEW

Both the Army and the Navy require that new research and substantive amendments to approved research must undergo review for scientific merit prior to ethics (IRB) review, and that review must be considered by the IRB. A sample scientific merit review form that may be used for this purpose is attached as Appendix 4 to these *Policies & Procedures*. [SECNAVINST 3900.39E]

3. ACTIVE DUTY MILITARY--PROTECTIONS AGAINST UNDUE INFLUENCE

[Click Here to Go to the Table of Contents](#)

Additional protections for military research subjects are in place to minimize undue influence. These include the following: Officers are not permitted to influence the decision of their subordinates; officers and senior non-commissioned officers may not be present at the time of recruitment; officers and senior noncommissioned officers have a separate opportunity to participate; and when recruitment involves a percentage of a unit, an independent ombudsman is present. [DoDI 3216.02]

4. PROVISIONS FOR RESEARCH-RELATED INJURY

Investigators must explain to subjects any provisions for medical care for research-related injury, and such provisions, if any, must be described in the consent process and document. [DoDI 3216.02]

5. REPORTING UNANTICIPATED PROBLEMS INVOLVING RISK TO SUBJECTS AND OTHERS (UPIRTSOs), INCLUDING ADVERSE EVENTS, AND RESEARCH RELATED INJURY

Report unanticipated problems, adverse events, research-related injury and suspensions or terminations of research. These problems and events must be reported in a timely manner to the Assistant Secretary of Defense for Research and Engineering (ASD(R&E)) and to the Georgia Tech Office of Research Integrity Assurance. [DoDI 3216.02]

6. RESEARCH MONITOR

A research monitor shall be appointed by name when appropriate for studies involving more than minimal risk to subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or IO for research involving human subjects determined to involve minimal risk. There may be more than one research monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board. [DoDI 3216.02]

The duties of the research monitor shall be determined on the basis of specific risks or concerns about the research. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis) and report their observations and findings to the IRB or a designated official. [DoDI 3216.02]

The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. [DoDI

3216.02]Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities. [DoDI 3216.02]

The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects. [DoDI 3216.02]

- **Department of the Air Force [AFRLI 40-402]**

In addition to the requirements under DoDI 3216.02, the duties of a Research Monitor include:

- Determining, with the concurrence of the IRB, the level of on-site research observation that is required for the level and type of risk(s). Depending on the nature of the risks involved during the experiment, a research observer may be required to be on call, in the same building, or continuously present and in communication with the subject.
- If research requires on-scene observation, and the research monitor is not required to personally provide this observation, but the research monitor is responsible to design an appropriate system to provide observation, and with the IRB must concur/approve. This includes selection and training of any research observer.
- Ensuring a mechanism exists that informs subjects of the advocacy role of research monitors and delineates a process by which subjects may contact the overall Research Monitor should they desire to do so.
- Reporting to the IRB and Department/Division Chief any adverse event involving a subject. Any research/ consultant should assist in determining actual or potential harm. The report should include the research monitor's recommendation as AFRLI40-402 21 APRIL 2016 21 to whether or not the protocol should be stopped pending further investigation or until the IRB can access the research monitor's report.

- Any medical research consultant will be credentialed or licensed as appropriate to the medical risks involved in the research.

7. ADDITIONAL SAFEGUARDS FOR RESEARCH CONDUCTED WITH INTERNATIONAL POPULATIONS

Special protections are required when research is proposed to be conducted with international populations. Research *that is conducted outside the United States and its territories and possessions* must also comply with applicable requirements of the foreign country and its national laws and requirements. [DoDI 3216.02]

• Department of the Air Force

The Air Force requires that human use research that is to be conducted in a country other than the United States must be reviewed and approved by an IRB or similar body in the country where the research will take place. Whenever possible, this committee should satisfy the IRB membership requirements outlined in 32 CFR 219.107. This IRB or ethics committee must be able to review the research and ensure that it is acceptable based on national and local requirements, standards, and norms. This committee must also be willing to serve in an oversight capacity to assist the AFRL IRB in any matters of compliance and oversight. The AFRL IRB must be provided with the informed consent documents in the native language, as well as a back-translated version for review. All international research, regardless of risk level or determination of exemption, must be reviewed and approved by AFMSA/SGE-C prior to research commencement. [AFRLI 40-402]

8. WAIVER OF CONSENT

• Uniform Service Code

Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance. The Secretary of Defense may waive the prohibition in this section with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws. [10 USC 980]

• Department of Defense (DoD)

If the research involves interventions or interactions with subjects, a waiver of consent or parental permission requires approval from the Secretary of Defense or the delegated Heads of the OSD and DoD Components. If the research participant does not meet the definition of

experimental subject, the IRB may provide a waiver of consent, if appropriate. [DoDI 3216.02]

• **Department of Navy (DON)**

Requests for waiver shall not be made directly to ASD (R&E), but should be coordinated through the DON institution supporting the research and the Director, DON HRPP. The Navy SG will review and, if appropriate, forward requests for waiver to the Secretary of the Navy (SECNAV). [SECNAVINST 3900.39E].

9. RESEARCH INVOLVING MINORS

Research involving human subjects conducted or supported by the Department of Defense that recruits children to be subjects must meet the additional relevant protections of subpart D of §45 CFR 46 unless otherwise modified by the DoD Instruction. [DoDI 3216.02]

• **Department of the Army [AR 70-25]**

Minors may participate as subjects when the following conditions are met:

1. The research is intended to benefit the subject, and any risk involved is justified by the expected benefit to the minor
2. The expected benefits are at least as favorable to the minor as those presented by available alternatives.
3. A legally authorized representative has been fully informed and voluntarily consents, in advance, for the minor to participate in the research.
4. The minor, if capable, has assented in writing. In determining whether the minor is capable of assenting, the HUC will consider the minor's age, maturity, and psychological state. The HUC may waive assent for some or all minors involved in the study if it determines that the:
 - a. Capability of some or all of the minors is so limited that they cannot be reasonably consulted, or
 - b. Procedure involved in the research holds out a prospect for direct benefit that is important to the health or well-being of the minor, and is available only in the context of research.

10. LIMITATIONS ON COMPENSATION FOR U. S. MILITARY PERSONNEL

The Dual Compensation Act prohibits an individual from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week. These limitations include limitation on dual compensation, which prohibit an individual from receiving pay or compensation for research during duty hours and US military personnel may be compensated for research

if the participant is involved in the research when not on duty. This prohibition applies to employees paid from either appropriated or non-appropriated funds, or a combination thereof, and includes temporary, part-time, and intermittent appointments. This law is not applicable to enlisted off-duty military personnel in relation to their military duty. [Dual Compensation Act and 24 U.S.C. 30]

- **Active Duty Federal Personnel**

Active duty federal personnel may receive up to \$50 per blood draw. However, active duty federal personnel cannot be compensated for general research participation other than blood draws. [DoDI 3216.02]

- **Off-Duty Federal Personnel**

Off-duty federal personnel may receive up to \$50 per blood draw. If the blood draw research is not federally funded, then the off-duty personnel may be compensated in a reasonable amount as approved by the IRB. Additionally, off-duty personnel may be compensated for general research in a reasonable amount as approved by the IRB. However, this compensation cannot come directly from a federal source. [DoDI 3216.02]

- **Non-Federal Personnel**

Non-federal personnel may receive up to \$50 per blood draw in DoD-funded research. Additionally, non-federal personnel may be compensated for general research in a reasonable amount as approved by the IRB. These funds can come directly from either federal or non-federal sources. [DoDI 3216.02]

11. SURVEY RESEARCH

Research involving the administration of surveys to, or interviews of, DoD personnel (military or civilian) may require DoD approval of the surveys or interview questions. This involves research where DoD personnel and civilian personnel (working with the DoD and/or spouses and family members of DoD personnel) are asked to complete surveys; not when researchers funded by the DoD are conducting surveys of non-DoD personnel. For instructions on surveying military personnel across branches of the Department of Defense, see DoDI 1100.13 at

<https://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodi/110013p.pdf>.

12. DRUGS, DEVICES AND BIOLOGICS, INVESTIGATIONAL TEST ARTICLES

Research involving human subjects using surveys, materials under the purview of the FDA, or individually identifiable health information may be subject to additional Federal or DoD requirements, such as those identified under 21 CFR 50, 56, 312, 600 and 812 (DoDI 3216.02). If your research is considered to be “an organized program of healthcare preventive therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military mission” (Force Health Protection Program), then additional regulations may apply under DoDI 6200.02.

- **Department of the Army**

The Army describes its requirements in Army Regulation 40-7, “Use of US Food and Drug Administration (FDA) Regulated Investigational Products in Humans Including Schedule 1 Controlled Substances. http://www.apd.army.mil/pdffiles/r40_7.pdf

- **Department of Navy (DON)**

All research involving the use of investigational test articles (drugs, devices and biologics) shall comply with U.S. Food and Drug Administration (FDA) regulations, references (i) through (m). An Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) must be filed with the FDA whenever research involving human subjects is conducted outside the United States with drugs, devices or biologics, which would require filing of an IND or an IDE if the research were conducted in the United States. Only the Navy SG, Commanders, and Commanding Officers may be designated as sponsors for INDs and IDEs. The Navy SG may consider an IND/IDE equivalency in circumstances where the requirements may not be possible or feasible in international research. Investigators may not be designated as sponsors for INDs and IDEs. [SECNAVINST 3900.39E]

13. PRISONERS OF WAR (POW), OTHER PRISONERS, AND DETAINEES

Research involving human subjects that includes prisoners or human subjects that become prisoners must meet the relevant protections of subpart C of 45CFR46 (DoDI 3216.02). The Georgia Tech IRB will promptly report all decisions involving prisoners as human subjects in research to the HRPO. In addition to the four categories of allowable research with prisoners, two additional conditions are allowable:

1. Epidemiological research that meets the following criteria can also be approved in accordance with the requirements of subpart C of Reference (h) and the requirements of this Instruction:

1. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor associations for a disease.
 2. The research presents no more than minimal risk.
 3. The research presents no more than an inconvenience to the human subject.
 4. Prisoners are not a particular focus of the research.
2. Research involving human subjects that would meet the criteria described at section 219.101(b) of Reference (c) can be conducted, but must be approved by a convened IRB and meet the requirements of subpart C of Reference (h), this Instruction, and other applicable requirements. [DoDI 3216.02]

- **Department of the Army**

Research with Prisoners of War (POWs) is prohibited. [AR 70-25]

14. ALLEGATIONS OF NON-COMPLIANCE WITH HUMAN RESEARCH PROTECTIONS

Allegations of non-compliance with DoDI 3216.02 will be properly investigated and reported to the DoD Component supporting the research. All findings of serious or continuing noncompliance with this Instruction that have been substantiated by inquiry or investigation shall be reported to the Assistant Secretary of Defense for Research and Engineering (ASD(R&E)) in a timely manner. [DoDI 3216.02]

- **Department of the Air Force, Department of the Army, and Department of the Navy**

All three departments require the convened IRB to review any serious and continuing non-compliance. The decision of the IRB and notification of the actions taken to remedy the non-compliance is then required to be reported to the IRB Committee, the Institutional Official, and the HRPO for the DoD Component involved in the research. [AFLRI 40-402; AR 70-25; SECNAVINST 3900.39E]

15. CONFLICTING AND COMPETING INTERESTS

Conflicts of interest, not limited to financial conflicts, must be identified and managed appropriately. [DoDI 3216.02; AFRLI 40-402; AR 70-25; SECNAVINST 3900.39E]

16. DOCUMENTATION AND OVERSIGHT THROUGH HEADQUARTERS-LEVEL REVIEW OF RESEARCH PROTOCOLS

A headquarters level or second level review is an additional requirement of the DoD that differs significantly from the NIH review process with which many awardees are familiar. Once a DoD supported study is either determined to be not human subjects research, exempt research involving human subjects, or reviewed and approved as non-exempt research, the study must undergo a HQ level or second level review that is coordinated by the human research oversight office of the DoD component (e.g., Army, Navy, Air Force, etc). Each DoD component has a unique process for accomplishing this required HQ level review. [DoDI 3216.02]

- **Department of the Air Force**

Protocols determined to involve minimal risk may begin once written approval from the GT IRB has been issued. The protocol and records of the approval will then be forwarded to AFMSA/SGE-C for their review and records, but may be subject to modifications or requests for additional information before research can begin.

Protocols determined to involve greater-than-minimal risk, non-lethal weapons, and international research requires approval by AFMSA/SGE-C before research can begin. [AFI 40-402]

- **Department of the Army**

The U.S. Army Medical Research and Materiel Command (USAMRMC) Headquarters' Office of Research Protections oversees the HQ second level review process for USAMRMC supported research. All USAMRMC supported research must be reviewed and approved by the HRPO prior to implementation. Certain research protocols may also be reviewed and approved by the Headquarters, USAMRMC Research Ethics Advisory Panel (REAP). The assigned HSPS will provide additional information for those projects that must be reviewed by the HQ USAMRMC REAP.

The USAMRMC has posted "*Information for Investigators: Headquarters, U. S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Regulatory Requirements – ORP Human Research Protection Office (HRPO)*" at

https://mrdc.amedd.army.mil/assets/docs/orp/hrpo_information_for_investigators.pdf.

Department of Navy (DON)

Protocols determined to involve minimal risk may begin once written approval from the GT IRB has been issued. The protocol and records of the approval will then be forwarded to the DON Human Research Protection Officials (HRPO) for their review and records, but may be subject to modifications or requests for additional information before research can begin.

Protocols determined to involve greater-than-minimal risk and international research requires approval by the DON HRPO before research can begin. [SECNAVINST 3900.39E]

17. AUDITS, INVESTIGATIONS OR INSPECTIONS OF DEPARTMENT OF NAVY-SUPPORTED RESEARCH

The DON must be notified of any audits, investigations or inspections of DON-supported research. Report the following to the DON Human Research Protections Program (HRPP) Office and appropriate sponsor(s): All suspensions or terminations of previously approved DON supported research protocols; the initiation and results of investigations of alleged noncompliance with human subject protections ; unanticipated problems involving risks to subjects or others, or serious adverse events in DON-supported research; all audits, investigations, or inspections of DON -supported research protocols; all audits, investigations, or inspections of the institution's HRPP conducted by outside entities (e.g., the FDA or OHRP); significant communication between institutions conducting research and other federal departments and agencies regarding compliance and oversight; all restrictions, suspensions, or terminations of institutions' assurances. Report the initiation of all investigations and report results, regardless of the findings, to the Navy Secretary General and appropriate sponsors. [SECNAVINST 3900.E]

18. PUBLICATIONS, PRESENTATIONS OR REPORTS BASED ON THE RESEARCH PROTOCOL

The PI should continue to submit publications, presentations or reports based on the research protocol after closure of the study

- **Department of Air Force**

Additionally, the Department of the Air Force requires that the IRB receive and maintain copies of publications, presentations or reports based on the research protocol. [AFRLI 40-402]

19. STUDY CLOSURE:

A study closure submission should be submitted to the IRB once all enrollment has ceased and all of the data has been completely de-identified.

- **Department of Air Force**

Additionally, the Department of the Air Force states that “a study cannot be closed by the IRB administrative office without a report from the PI confirming that research is complete and there is no further interaction with human subjects or PII data.” [AFRLI 40-402]

20. RECORD RETENTION:

The Department of Defense, Component of the Department of Defense, and other auditing agencies may require access to or submission of study records. These records include, but are not limited to: IRB meeting minutes, IRB reviews, IRB decisions, audit reports, study protocol, informed consent, copies of signed informed consent, data, and any other documents used during the study. DoD regulations require that all records are to be retained for a minimum of 3 years after the completion of the research. Other Federal regulations and local policies regarding records must also be followed, as appropriate.

21. PRINCIPAL INVESTIGATOR ACTIONS:

When a research protocol is subject to the DOD Addendum, the IRB letter of approval will contain additional guidance for the Principal Investigator, as follows:

IMPORTANT NOTICE

This study is subject to the Department of Defense (DOD) Addendum to the Georgia Tech Federalwide Assurance (FWA) of Compliance for the Protection of Human Subjects and therefore must be in compliance with DOD-specific requirements and stipulations.

In particular, please note:

DOD COMPLIANCE CONCURRENCE MUST BE OBTAINED BEFORE WORK WITH HUMAN SUBJECTS MAY BEGIN, DESPITE GEORGIA TECH IRB APPROVAL BEING ISSUED.

DOD compliance concurrence is not another IRB review; rather, it is a process by which the DOD Human Research Protection Official (HRPO) ensures compliance with all applicable regulations and ascertains whether to concur with the civilian IRB's determination.

Obtaining DOD compliance concurrence is the responsibility of the Principal Investigator.

DOD compliance concurrence must be documented in the Georgia Tech IRB record.

Within 60 days of the date of this letter, please upload the DOD notice of compliance concurrence and any relevant DOD correspondence to the protocol in IRBWISE.

This must be done prior to starting work with human subjects.

Some of the military components impose additional and varying agency-specific requirements before authorizing work with human subjects to begin. During review of your study, the Georgia Tech IRB contemplated the additional requirements of which we are aware, and those were communicated to you during the review process.

Appendix 4: Scientific Review Template for DOD Protocols

<p>Georgia Institute of Technology Scientific Review Template for conducting independent scientific review of human subjects protocols involving the US Army or Department of the Navy</p>			
<p><i>The US Army and the Navy require that protocols must be scientifically sound prior to review by the institutional review board (IRB); therefore, investigators must address the requirements of the scientific review before proposals are forwarded to the IRB for consideration of human subject protection issues.</i></p>			
Principal Investigator:		Date of Review:	
Title of Research Protocol:			
SCIENTIFIC REVIEW			
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the entire proposal well written, logical, and clear? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the research question articulated with clarity and precision? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the research question relevant to Army or Navy Medicine? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Does the background section inform us why this question is important? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the literature search comprehensive and complete? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the proposed design appropriate for the research question being asked? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Are the controls adequate? Comments:		
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is it likely that this design will produce a credible answer to the research question? Comments:		
FEASIBILITY			
<input type="checkbox"/> Yes <input type="checkbox"/> No	Are the research methods feasible? Comments:	<input type="checkbox"/> Yes <input type="checkbox"/> No	In the time frame proposed? Comments:

<input type="checkbox"/> Yes <input type="checkbox"/> No	By the personnel who will carry out the study? Comments:	<input type="checkbox"/> Yes <input type="checkbox"/> No	With the resources that are available or requested? Comments:
SAMPLE SIZE			
<input type="checkbox"/> Yes <input type="checkbox"/> No	Are the sample size calculations presented (if needed)? Comments:	<input type="checkbox"/> Yes <input type="checkbox"/> No	Are they credible? Comments:
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the proposed statistical analysis valid? Comments:		
RECOMMENDATION			
<input type="checkbox"/> Yes <input type="checkbox"/> No	Is the proposal endorsed for its science?		
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> With changes	Do you recommend this proposal for referral to the Institutional Review Board for consideration of human subject protection issues? If NO or WITH CHANGES, please elaborate:		
Reviewer's Name PRINTED		Reviewer's Signature:	
<i>This completed form should be uploaded to the protocol as a Supplemental Document in IRBWISE.</i>			

Appendix 5: Nanotechnology Guidance

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology Guidance for Industry

DRAFT GUIDANCE
U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner
June 2011

TABLE OF CONTENTS

I. INTRODUCTION

II. SCOPE

III. DISCUSSION

A. Points to Consider

B. Rationale for Elements Within the Points to Consider

1. *Engineered material or end product*
2. *At least one dimension in the nanoscale range (approximately 1 nm to 100 nm)*
3. *Exhibits properties or phenomena . . . that are attributable to its dimension(s)*
4. *Size range of up to one micrometer (1,000 nm)*

IV. CONCLUSION

Guidance for Industry [1]

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

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

I. INTRODUCTION

This guidance is intended for manufacturers, suppliers, importers and other stakeholders. The guidance describes FDA's current thinking on whether FDA-regulated products [2] contain nanomaterials or otherwise involve the application of nanotechnology.

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

II. SCOPE

This guidance document does not establish any regulatory definitions. Rather, it is intended to help industry and others identify when they should consider potential implications for regulatory status, safety, effectiveness, or public health impact that may arise with the application of nanotechnology in FDA-regulated products. Public input on the guidance may also inform the development of any regulatory definitions in the future, as needed.

[Click Here to Go to the Table of Contents](#)

Nor does this guidance document address the regulatory status of products that contain nanomaterials or otherwise involve the application of nanotechnology, which are currently addressed on a case-by-case basis using FDA's existing review processes.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful.

In the future, FDA may issue additional guidance documents to address considerations for specific products or classes of products, consistent with the "[Principles for Regulation and Oversight of Emerging Technologies](#)"² released March 11, 2011 as well as the "[Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials](#)"³ released on June 9, 2011, that were issued jointly by the Office of Science and Technology Policy, Office of Management and Budget, and the United States Trade Representative. [3]

III. DISCUSSION

FDA has not to date established regulatory definitions of "nanotechnology," "nanoscale" or related terms. [4] However, there are numerous definitions of "nanotechnology." The term is perhaps most commonly used to refer to the engineering (i.e., deliberate manipulation, manufacture or selection) of materials that have at least one dimension in the size range of approximately 1 to 100 nanometers. For example, the National Nanotechnology Initiative Program defines nanotechnology as "the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications." [5] Other factors such as function, shape, charge, the ratio of surface area to volume, or other physical or chemical properties have also been mentioned in various published definitions.

As a first step toward developing FDA's framework for considering whether FDA-regulated products include nanomaterials or otherwise involve nanotechnology, the agency has developed the points discussed below. Based on FDA's current scientific and technical understanding of nanomaterials and their characteristics, FDA believes that evaluations of safety, effectiveness or public health impact of such products should consider the unique properties and behaviors that nanomaterials may exhibit. These points to consider are intended to be broadly applicable to all FDA-regulated products, with the understanding that additional guidance may be articulated for specific product areas, as appropriate in the future.

4. Points to Consider

At this time, when considering whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask:

1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or
2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.

These considerations apply not only to new products, but also may apply when manufacturing changes alter the dimensions, properties, or effects of an FDA-regulated product or any of its

components. Additionally, they are subject to change in the future as new information becomes available, and to refinement in future product-specific guidance documents.

B. Rationale for Elements within the Points to Consider

1. Engineered material or end product

This term is used to distinguish between products that have been engineered to contain nanoscale materials or involve the application of nanotechnology from those products that contain incidental or background levels of nanomaterials or those that contain materials that naturally occur in the nanoscale range. FDA is particularly interested in the *deliberate* manipulation and control of particle size to produce specific properties, because the emergence of these new properties or phenomena may warrant further evaluation. This is distinct from the more familiar use of biological or chemical substances that may naturally exist at small scales, including at the nanoscale, such as microorganisms or proteins.

U. At least one dimension in the nanoscale range (approximately 1 nm to 100 nm)

A size range of approximately 1 nm to 100 nm is commonly used in various working definitions or descriptions proposed by the regulatory and scientific community. [6] In this size range, materials can exhibit new or altered physicochemical properties which enable novel applications. [7] Accordingly, a range of approximately 1 nm to 100 nm should be applied as a first reference point in considering whether an FDA-regulated product contains nanomaterials or otherwise involves application of nanotechnology.

U. Exhibits properties or phenomena . . . that are attributable to its dimension(s)

These terms are used because properties and phenomena of materials at the nanoscale enable applications that can affect safety, effectiveness, performance, quality and, where applicable, public health impact of FDA-regulated products. For example, dimension-dependent properties or phenomena may be used for functional effects such as increased bioavailability, decreased dosage, or increased potency of a drug product [8], decreased toxicity of a drug product [9], better detection of pathogens [10], enhanced protection offered by improved food packaging materials [11], or improved delivery of a functional ingredient or a nutrient in food [12]. The properties and phenomena may be due to altered chemical, biological, or magnetic properties, altered electrical or optical activity, increased structural integrity, or other unique characteristics of nanoscale materials not normally observed in their larger counterparts. [13] These changes may raise questions about the safety, effectiveness, performance, quality or public health impact of the products. In addition, considerations such as routes of exposure, dosage, and behavior in various biological systems (including specific tissues and organs) are critical for evaluating the wide array of products under FDA's jurisdiction.

U. Size range of up to one micrometer (1,000 nm)

Materials or end products can also exhibit properties or phenomena attributable to a dimension(s) above the approximate 100 nm range. A reduction in size can lead to properties that are clearly different from those of the conventionally-scaled material although the material or end product itself may not necessarily be within the nanoscale range. Structures such as agglomerates and aggregates are of interest in this context [14] as are coated, functionalized, or hierarchically assembled structures [15]. To account for such materials, some definitions of nanomaterial have applied the 100 nm upper dimension to the *internal* structure [16]. In the absence of a bright line as to where an upper limit should be set, the agency considers that an upper bound of one micrometer (i.e., 1,000 nm) would serve as a reasonable parameter for screening materials with dimensions beyond the nanoscale range for further examination to determine whether these materials exhibit properties or phenomena

[Click Here to Go to the Table of Contents](#)

attributable to their dimension(s) and relevant to nanotechnology. [17] The agency believes that the one micrometer upper limit in the second point to consider serves both to (1) exclude macro-scaled materials that may have properties attributable to their dimension(s) but are not likely relevant to nanotechnology; and (2) include those materials (such as aggregates, agglomerates, or coated, functionalized, or hierarchically assembled structures) with dimension(s) above 100 nm that may exhibit dimension-dependent properties or phenomena relevant to nanotechnology and distinct from those of macro-scaled materials.

IV. CONCLUSION

There is a critical need to learn more about the potential role and importance of dimensions in the characteristics exhibited by engineered nanomaterials that may be used in producing products regulated by FDA. Premarket review, when required, offers an opportunity to better understand the properties and behavior of products that contain engineered nanomaterials or otherwise involve application of nanotechnology. And where products applying nanotechnology are not subject to premarket review, the agency urges manufacturers to consult with the agency early in the product development process. In this way, any questions related to the regulatory status, safety, effectiveness, or public health impact of these products can be appropriately and adequately addressed.

Footnotes

1. The points to consider presented in this guidance have been prepared by the U.S. Food and Drug Administration's Nanotechnology Task Force (Task Force). The Task Force, formed in August 2006, was charged with determining regulatory approaches that would enable the continued development of innovative, safe, and effective FDA-regulated products that use nanoscale materials.

2. The use of the word "products" in this guidance document is meant to include products, materials, ingredients and other substances regulated by FDA.

3. <http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf>; <http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf>

4. In the 2007 Report, the FDA Nanotechnology Task Force stated: "The Task Force believes FDA should continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science. Moreover, while one definition for "nanotechnology," "nanoscale material," or related term or concept may offer meaningful guidance in one context, that definition may be too narrow or broad to be of use in another. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform the agency's judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products" (Nanotechnology. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007, page 6-7; available online at: <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm>)

5. National Nanotechnology Initiative Website, <http://www.nano.gov/nanotech-101/what>.

6. For example, a size range of approximately 1 nm to 100 nm is used in definitions, working definitions, or descriptions published by the National Nanotechnology Initiative; Environmental Protection Agency; European Scientific Committee on Consumer Products; European Commission; Health Canada; International Standards Organization; Organization for Economic Cooperation and Development's Working Party on Nanotechnology and Working Party on Manufactured Nanomaterials; National Cancer Institute; and American National Standards Institute.

*7. National Nanotechnology Initiative Website, <http://www.nano.gov/nanotech-101/what>; Powers KW, Brown SC, Krishna VB, et al. Research Strategies for Safety Evaluation of Nanomaterials. Part VI. Characterization of Nanoscale Particles for Toxicological Evaluation. *Toxicological Sciences* 90: 296–303, 2006.*

*8. Merisko-Liversidge EM and Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. *Toxicologic Pathology*, 36:43-48, 2008.*

*9. Paciotti GF, Myer L, Weinreich D, et al. Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. *Drug Delivery*, 11:169-183, 2004.*

*10. Kaittanis C, Santra S, Manuel PJ. Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. *Advanced Drug Delivery Reviews* 62:408-423, 2010.*

[Click Here to Go to the Table of Contents](#)

- 11. Chaudhry Q, Scotter M, Blackburn J, et al. Applications and implications of nanotechnologies for the food sector. Food Additives and Contaminants 25:241-258, 2008.*
- 12. IOM (Institute of Medicine). Nanotechnology in food products: Workshop Summary. Washington, DC: The National Academies Press, 2009; Chen L, Remondetto GE, Subirade M. Food protein-based materials as nutraceutical delivery systems. Trends in Food Science & Technology 17:272-283, 2006.*
- 13. Nanotechnology. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007; available online at: <http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm>⁹).*
- 14. Considerations on a Definition of Nanomaterial for Regulatory Purposes, Joint Research Centre, 2010; available online at: http://ec.europa.eu/dqs/jrc/downloads/jrc_reference_report_201007_nanomaterials.pdf¹⁰.*
- 15. Scientific Basis for the Definition of the Term “Nanomaterial”, Scientific Committee on Emerging and Newly Identified Health Risks, July 6, 2010; available online at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_030.pdf¹¹.*
- 16. ISO Technical Specification on Nanotechnologies – Vocabulary – Part 1: Core terms (ISO/TS 80004-1:2010); European Commission draft recommendation on the definition of the term “nanomaterial” (October, 2010).*
- 17. Including materials of interest with dimension(s) beyond 100 nm is consistent with the recent conclusions presented by the Joint Research Centre and the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission: “In order to base a nanomaterials definition for regulatory purposes on size alone, the upper nanoscale limit should ideally be high enough to capture all types of materials that would need particular attention for regulation due to their nanoscale size. Upper limits which are often used in existing definitions, for example 100 nm, may require the introduction of one or more qualifiers based on structural features or properties other than size, in order to capture structures of concern (for example agglomerates or aggregates) with a size larger than 100 nm in the regulation” (Considerations on a Definition of Nanomaterial for Regulatory Purposes, Joint Research Centre, 2010); “The upper size limit for one or more external dimensions of 100 nm is complicated by the potential exclusion of aggregates, agglomerates and multicomponent assemblies that would have external sizes greater than this” (Scientific Basis for the Definition of the Term “Nanomaterial”, Scientific Committee on Emerging and Newly Identified Health Risks, July 6, 2010); “An upper limit of 100 nm is commonly used by general consensus but there is no scientific evidence to qualify the appropriateness of this value (Stated as SCENIHR conclusions in the EC draft recommendation on the definition of term “nanomaterial”, October 2010; available online at: http://ec.europa.eu/environment/consultations/pdf/recommendation_nano.pdf¹²). In addition, ISO “acknowledged that health and safety considerations associated with intentionally produced and incidental nano-objects do not abruptly end at dimensions of 100 nm” (ISO/TS 80004-1:2010).*

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)

**Appendix 6: FDA Guidance for Sponsors, Clinical Investigators, and IRBs
Regarding FDA Form 1572**

Guidance for Industry

**Investigator Responsibilities — Protecting the Rights,
Safety, and Welfare of Study Subjects**

**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)
Center for Devices and Radiological Health (CDRH)**

**Procedural
October 2009**

Guidance for Industry

Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects

*Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
(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
Food and Drug Administration
<http://www.fda.gov/cber/guidelines.htm>.
(Tel) 800-835-4709 or 301-827-1800*

or

*Office of Health and Industry Programs
Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
Tel: 1-800-638-2041
www.fda.gov/cdrh*

**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)
Center for Devices and Radiological Health (CDRH)**

Procedural

October 2009

Contains Nonbinding Recommendations

TABLE OF CONTENTS

I. INTRODUCTION.....	1
II. OVERVIEW OF INVESTIGATOR RESPONSIBILITIES.....	1
III. CLARIFICATION OF CERTAIN INVESTIGATOR RESPONSIBILITIES.....	2
A. SUPERVISION OF THE CONDUCT OF A CLINICAL INVESTIGATION.....	2
1. <i>What Is Appropriate Delegation of Study-Related Tasks?.....</i>	<i>3</i>
2. <i>What Is Adequate Training?.....</i>	<i>4</i>
3. <i>What Is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?.....</i>	<i>4</i>
4. <i>What Are an Investigator’s Responsibilities for Oversight of Other Parties Involved in the Conduct of a Clinical Trial?.....</i>	<i>5</i>
B. PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF STUDY SUBJECTS.....	7
1. <i>Reasonable Medical Care Necessitated by Participation in a Clinical Trial.....</i>	<i>7</i>
2. <i>Reasonable Access to Medical Care.....</i>	<i>7</i>
3. <i>Protocol Violations that Present Unreasonable Risks.....</i>	<i>8</i>
ATTACHMENT A: COPY OF FORM 1572.....	9
ATTACHMENT B: INVESTIGATOR RESPONSIBILITIES.....	12

Contains Nonbinding Recommendations

Guidance for Industry¹

Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects

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

I. INTRODUCTION

This guidance provides an overview of the responsibilities of a person who conducts a clinical investigation of a drug, biological product, or medical device (an *investigator* as defined in 21 CFR 312.3(b) and 21 CFR 812.3(i)). The goal of this guidance is to help investigators better meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations. This guidance is intended to clarify for investigators and sponsors FDA's expectations concerning the investigator's responsibility (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and (2) to protect the rights, safety, and welfare of study subjects.

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

II. OVERVIEW OF INVESTIGATOR RESPONSIBILITIES

In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible for:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care
- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

Contains Nonbinding Recommendations

Although specific investigator responsibilities in drug and biologics clinical trials are not identical to the investigator responsibilities in medical device clinical trials, the general responsibilities are

¹ This guidance has been prepared by the Investigator Responsibilities Working Group, which includes representatives from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

essentially the same. This guidance discusses the general investigator responsibilities that are applicable to clinical trials of drugs, biologics, and medical devices.

An investigator's responsibilities in conducting clinical investigations of **drugs** or **biologics** are provided in 21 CFR Part 312. Many of these responsibilities are included in the required investigator's signed statement, Form FDA-1572 (see Attachment A) (hereinafter referred to as 1572). Note that although the 1572 specifically incorporates most of the requirements directed at investigators in part 312, not all requirements are listed in the 1572. Investigators and sponsors should refer to 21 CFR Parts 11, 50, 54, 56, and 312 for a more comprehensive listing of FDA's requirements for the conduct of drug and biologics studies.²

An investigator's responsibilities in conducting clinical investigations of a **medical device** are provided in 21 CFR Part 812, including the requirement that there be a signed agreement between the investigator and sponsor (see 21 CFR 812.43(c)(4) and 812.100). The medical device regulations do not require use of a specific form for an investigator's statement; and there are additional requirements not listed above (see Attachment B). Investigators and sponsors should refer to 21 CFR Parts 11, 50, 54, 56, and 812 for a more comprehensive listing of FDA's requirements for the conduct of device studies.

Nothing in this guidance is intended to conflict with recommendations for investigators contained in the International Conference on Harmonisation (ICH) guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance* (Good Clinical Practice Guidance).³

III. CLARIFICATION OF CERTAIN INVESTIGATOR RESPONSIBILITIES

This section of the guidance clarifies the investigator's responsibility to supervise the conduct of the clinical investigation and to protect the rights, safety, and welfare of participants in drug and medical device clinical trials.

A. Supervision of the Conduct of a Clinical Investigation

As stated above, investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312, commit themselves to personally conduct or supervise the investigation. Investigators who conduct clinical investigations of medical devices, under 21 CFR Part 812, commit themselves to supervise all testing of the device involving human subjects. It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

² As a reminder, some investigators may be responsible for submitting certain clinical trial information to the National Institutes of Health clinical trials data bank under 42 U.S.C 282(j), 402(j) of the Public Health Service Act. Although not all investigators will be expected to meet this requirement, go to www.clinicaltrials.gov for further information about potential responsibilities.

³ Guidances, including ICH guidances, are available on the Agency's Web page. See the Web addresses on the second title page of this guidance.

In assessing the adequacy of supervision by an investigator, FDA focuses on four major areas: (1) whether individuals who were delegated tasks were qualified to perform such tasks, (2) whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study, (3) whether there was adequate supervision and involvement in the ongoing conduct of the study, and (4) whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

1. What Is Appropriate Delegation of Study-Related Tasks?

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task. Appropriate delegation is primarily an issue for tasks considered to be clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing medical care to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Licensing requirements may vary by jurisdiction (e.g., states, countries). Investigators should take such qualifications/licensing requirements into account when considering delegation of specific tasks. In all cases, a qualified physician (or dentist) should be responsible for all trial-related medical (or dental) decisions and care.⁴

During inspections of investigation sites, FDA has identified instances in which study tasks have been delegated to individuals lacking appropriate qualifications. Examples of tasks that have been inappropriately delegated include:

- Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria
- Physical examinations
- Evaluation of adverse events
- Assessments of primary study endpoints
- Obtaining informed consent

The investigator is responsible for conducting studies in accordance with the protocol (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). In some cases a protocol may specify the qualifications of the individuals who are to perform certain protocol-required tasks (e.g., physician, registered nurse), in which case the protocol must be followed even if state law permits individuals with different qualifications to perform the task (see 21 CFR 312.23(a)(6) and 312.40(a)(1)). For example, if the state in which the study site is located permits a nurse practitioner or physician's assistant to perform physical examinations under the supervision of a physician, but the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated.⁵ This list should also describe the delegated tasks, identify

⁴ Guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance*, section 4.3.1.

⁵ *Ibid*, section 4.1.5

the training that individuals have received that qualifies them to perform delegated tasks (e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

2. What Is Adequate Training?

The investigator should ensure that there is adequate training for all staff participating in the conduct of the study, including any new staff hired after the study has begun to meet unanticipated workload or to replace staff who have left. The investigator should ensure that staff:

- Are familiar with the purpose of the study and the protocol
- Have an adequate understanding of the specific details of the protocol and attributes of the investigational product needed to perform their assigned tasks
- Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials and the protection of human subjects
- Are competent to perform or have been trained to perform the tasks they are delegated
- Are informed of any pertinent changes during the conduct of the trial and receive additional training as appropriate

If the sponsor provides training for investigators in the conduct of the study, the investigator should ensure that staff receive the sponsor's training, or any information (e.g., training materials) from that training that is pertinent to the staff's role in the study.

3. What Is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?

For each study site, there should be a distinct individual identified as an investigator who has supervisory responsibility for the site. Where there is a subinvestigator at a site, that individual should report directly to the investigator for the site (i.e., the investigator should have clear responsibility for evaluating the subinvestigator's performance and the authority to terminate the subinvestigator's involvement with the study) and the subinvestigator should not be delegated the primary supervisory responsibility for the site.

The investigator should have sufficient time to properly conduct and supervise the clinical trial. The level of supervision should be appropriate to the staff, the nature of the trial, and the subject population. In FDA's experience, the following factors may affect the ability of an investigator to provide adequate supervision of the conduct of an ongoing clinical trial at the investigator's site:

- Inexperienced study staff
- Demanding workload for study staff
- Complex clinical trials (e.g., many observations, large amounts of data collected)
- Large number of subjects enrolled at a site
- A subject population that is seriously ill
- Conducting multiple studies concurrently
- Conducting a study from a remote (e.g., off-site) location
- Conducting a study at multiple sites under the oversight of a single investigator, particularly where those sites are not in close proximity

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. A plan might include the following elements, to the extent they apply to a particular trial:

- Routine meetings with staff to review trial progress, adverse events, and update staff on any changes to the protocol or other procedures
- Routine meetings with the sponsor's monitors
- A procedure for the timely correction and documentation of problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
- A procedure for documenting or reviewing the performance of delegated tasks in a satisfactory and timely manner (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
- A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation and the risks
- A procedure for ensuring that source data are accurate, contemporaneous, and original
- A procedure for ensuring that information in source documents is accurately captured on the case report forms (CRFs)
- A procedure for dealing with data queries and discrepancies identified by the study monitor
- Procedures for ensuring study staff comply with the protocol and adverse event assessment and reporting requirements
- A procedure for addressing medical and ethical issues that arise during the course of the study in a timely manner

4. What Are an Investigator's Responsibilities for Oversight of Other Parties Involved in the Conduct of a Clinical Trial?

a. Study Staff Not in the Direct Employ of the Investigator

Staff involved directly in the conduct of a clinical investigation may include individuals who are not in the direct employ of the investigator. For example, a site management organization (SMO) may hire an investigator to conduct a study and provide the investigator with a study coordinator or nursing staff employed by the SMO. In this situation, the investigator should take steps to ensure that the staff not under his/her direct employ are qualified to perform delegated tasks (see section III.A.1) and have received adequate training on carrying out the delegated tasks and on the nature of the study (see section III.A.2), or the investigator should provide such training. The investigator should be particularly cautious where documentation needed to comply with the investigator's regulatory responsibilities is developed and maintained by SMO staff (e.g., source documents, CRFs, drug storage and accountability records, institutional review board correspondence). A sponsor who retains an SMO shares responsibility for the quality of the work performed by the SMO.

The investigator is responsible for supervising the study tasks performed by this staff, even though they are not in his/her direct employ during the conduct of the study (see section III.A.3). This responsibility exists regardless of the qualifications and experience of staff members. In the event that the staff's performance of study-related tasks is not adequate and cannot be made satisfactory by the investigator, the investigator should document the observed deficiencies in writing to the staff

member's supervisor(s) and inform the sponsor. Depending on the severity of the deficiencies, the clinical trial may need to be voluntarily suspended until personnel can be replaced.

b. Parties Other than Study Staff

There are often critical aspects of a study performed by parties not involved directly in patient care or contact and not under the direct control of the clinical investigator. For example, clinical chemistry testing, radiologic assessments, and electrocardiograms are commonly done by a central independent facility retained by the sponsor. Under these arrangements, the central facility usually provides the test results directly to the sponsor and to the investigator. Because the activities of these parties are critical to the outcome of the study and because the sponsor retains the services of the facility, the sponsor is responsible for ensuring that these parties are competent to fulfill and are fulfilling their responsibilities to the study.

Less frequently, a study may require that investigators arrange to obtain information critical to the study that cannot be obtained at the investigator's site. For example, if the study protocol requires testing with special equipment or expertise not available at the investigator's site, the investigator might make arrangements for an outside facility to perform the test. In this case, the results are usually provided directly to the investigator, who then submits the information to the sponsor. If the investigator retains the services of a facility to perform study assessments, the investigator should take steps to ensure that the facility is adequate (e.g., has the required certification or licenses). The investigator may also institute procedures to ensure the integrity of data and records obtained from the facility providing the information (e.g., a process to ensure that records identified as coming from the facility are authentic and accurate). Procedures are particularly important when assessments are crucial to the evaluation of the efficacy or safety of an intervention or to the decision to include or exclude subjects who would be exposed to unreasonable risk.

Investigators should carefully review the reports from these external sources for results that are inconsistent with clinical presentation. To the extent feasible, and considering the specifics of study design, investigators should evaluate whether results appear reasonable, individually, and in aggregate, and they should document the evaluation. If investigators detect possible errors or suspect that results from a central laboratory or testing facility might be questionable, the investigator should contact the sponsor immediately.

c. Special Considerations for Medical Device Studies

Field clinical engineers (device sponsor employees) have traditionally played a role in some investigational device procedures (e.g., cardiology, orthopedics, and ophthalmology) by providing technical assistance to the device investigator. The field clinical engineer should be supervised by the investigator because the field clinical engineer's presence or activities may have the potential to bias the outcome of studies, may affect the quality of research data, and/or may compromise the rights and welfare of human subjects. The field clinical engineer's activities should be described in the protocol. If the field engineer has face-to-face contact with subjects or if the activities of the field engineer directly affect the subject, those activities should also be described in the informed consent.

B. Protecting the Rights, Safety, and Welfare of Study Subjects

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). This responsibility should include:

- Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
- Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
- Adhering to the protocol so that study subjects are not exposed to unreasonable risks

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.

1. Reasonable Medical Care Necessitated by Participation in a Clinical Trial

During a subject's participation in a trial, the investigator (or designated subinvestigator) should ensure that reasonable medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial participation. If the investigator does not possess the expertise necessary to provide the type of medical care needed by a subject, the investigator should make sure that the subject is able to obtain the necessary care from a qualified practitioner. For example, if the study involves placement of a carotid stent by an interventional neuroradiologist and the subject suffers a cerebral stroke, the neuroradiologist should assess the clinical status of the subject and arrange for further care of the subject by a neurologist. Subjects should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention that develops during or after the course of their participation in a study, even if the follow-up period extends beyond the end of the study at the investigative site.

The investigator should also 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. For example, if the investigator determines that the subject has had an exacerbation of an existing condition unrelated to the investigational product or the disease or condition under study, the investigator should inform the subject. The subject should also be advised to seek appropriate care from the physician who was treating the illness prior to the study, if there is one, or assist the subject in obtaining needed medical care.

2. Reasonable Access to Medical Care

Investigators should be available to subjects during the conduct of the trial for medical care related to participation in the study. Availability is particularly important when subjects are receiving a drug that has significant toxicity or abuse potential. For example, if a study drug has potentially fatal toxicity, the investigator should be readily available by phone or other electronic communication 24 hours a day and in reasonably close proximity to study subjects (e.g., not in another state or on prolonged travel). Study subjects should be clearly educated on the possible need for such contact and on precisely how to obtain it, generally by providing pertinent phone numbers, e-mail addresses, and other contact information, in writing. Prior to undertaking the conduct of a study, prospective investigators should consider whether they can be available to the extent needed given the nature of the trial.

During any period of unavailability, the investigator should delegate responsibility for medical care of study subjects to a specific qualified physician who will be readily available to subjects during that time (in the manner a physician would delegate responsibility for care in clinical practice). If the investigator is a non-physician, the investigator should make adequate provision for any necessary medical care that the investigator is not qualified to provide.

3. Protocol Violations that Present Unreasonable Risks

There are occasions when a failure to comply with the protocol may be considered a failure to protect the rights, safety, and welfare of subjects because the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks (e.g., enrolling a subject with decreased renal function in a trial in which decreased function is exclusionary because the drug may be nephrotoxic) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Similarly, failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that causes neutropenia) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Investigators should seek to minimize such risks by adhering closely to the study protocol.

ATTACHMENT A: COPY OF FORM 1572

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	Form Approved: OMB No. 0910-0014. Expiration Date: May 31, 2009. <i>See OMB Statement on Reverse.</i>
STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312) (See instructions on reverse side.)	NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).
1. NAME AND ADDRESS OF INVESTIGATOR	
2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED. <div style="display: flex; justify-content: space-around;"> ___ CURRICULUM VITAE ___ OTHER STATEMENT OF QUALIFICATIONS </div>	
3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATIONS(S) WILL BE CONDUCTED	
4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.	
5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE INVESTIGATION(S)	

6. NAMES OF THE SUBINVESTIGATORS (e.g., *research fellows, residents, associates*) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S)

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

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.

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.

9. COMMITMENTS:

I agree to 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, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to 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.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.

I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.

Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

**INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:**

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

<p>INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.</p>		
<p>10. SIGNATURE OF INVESTIGATOR</p>		<p>11. DATE</p>
<p>(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)</p>		
<p>Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>		
<p>Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266</p>	<p>Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-99) 1401 Rockville Pike Rockville, MD 20852-1448</p>	<p>"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number." "</p>
<p>Please DO NOT RETURN this application to this address.</p>		

ATTACHMENT B: INVESTIGATOR RESPONSIBILITIES FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS

This document is intended to assist investigators in identifying and complying with their responsibilities in connection with the conduct of clinical investigations involving medical devices. Although this guidance primarily addresses duties imposed upon clinical investigators by regulations of the Food and Drug Administration (FDA), investigators should be cognizant of additional responsibilities that may derive from other sources (such as the study protocol itself, the investigator agreement, any conditions of approval imposed by FDA or the governing institutional review board, as well as institutional policy and state law).

GENERAL RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.100)

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations
2. Protecting the rights, safety, and welfare of subjects under the investigator's care
3. Controlling devices under investigation
4. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50 and that the study is not commenced until FDA and IRB approvals have been obtained.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.110)

1. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation
2. Conducting the investigation in accordance with:
 - a. The signed agreement with the sponsor
 - b. The investigational plan
 - c. The regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations
 - d. Any conditions of approval imposed by an IRB or FDA

3. Supervising the use of the investigational device. 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 21 CFR Part 812 to receive it.
4. Disposing of the device properly. 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.

MAINTAINING RECORDS (21 CFR 812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA
2. Records of receipt, use or disposition of a device that relate to:
 - a. The type and quantity of the device, dates of receipt, and batch numbers or code marks
 - b. Names of all persons who received, used, or disposed of each device
 - c. The number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore
3. Records of each subject's case history and exposure to the device, including:
 - a. 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
 - b. All relevant observations, including records concerning adverse device effects (whether anticipated or not), 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;
 - c. 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

INSPECTIONS (21 CFR 812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.

SUBMITTING REPORTS (21 CFR 812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. To the sponsor and the IRB:

- Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)
- *Progress reports* on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)
- Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)
- Any use of the device *without obtaining informed consent*. (Due within 5 working days after such use.)
- A *final report*. (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")
- Any *further information* requested by FDA or the IRB about any aspect of the investigation.

2. To the Sponsor:

- *Withdrawal of IRB approval* of the investigator's part of an investigation. (Due within 5 working days of such action).

INVESTIGATIONAL DEVICE DISTRIBUTION AND TRACKING

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it (21 CFR 812.110(c)). The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of devices. Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (21 CFR 812.110(e)). Investigators must also maintain complete, current, and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140(a)(2)). Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

PROHIBITION OF PROMOTION AND OTHER PRACTICES (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and

[Click Here to Go to the Table of Contents](#)

investigators (or any person acting on behalf of a sponsor or investigator) and encompasses the following activities:

1. Promotion or test marketing of the investigational device
2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling
3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective
4. Representing that the device is safe or effective for the purposes for which it is being investigated

**Appendix 7: Frequently Asked Questions, Statement of Investigator
(Form FDA 1572)**

**Information Sheet
Guidance for
Sponsors, Clinical
Investigators, and
IRBs
Frequently Asked Questions
– Statement of Investigator
(Form FDA 1572)**

**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 2010**

Procedural Contains Nonbinding Recommendations

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

Additional copies are available from:

Office of Good Clinical Practice

Office of the Commissioner

*<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>
and/or*

Office of Communications

Division of Drug Information, WO51, Room 2201

10903 New Hampshire Ave.

Silver Spring, MD 20993

Phone: 301-796-3400; Fax: 301-847-8714

druginfo@fda.hhs.gov

*<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
and/or*

*Office of Communication, Outreach and
Development, HFM-40*

Center for Biologics Evaluation and Research

Food and Drug Administration

1401 Rockville Pike, Rockville, MD 20852-1448

*<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
(Tel) 800-835-4709 or 301-827-1800*

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

May 2010

Procedural Contains Nonbinding Recommendations

TABLE OF CONTENTS

I. GENERAL.....	4
1. What is the Statement of Investigator, Form FDA 1572?.....	4
2. Why does this form need to be completed by an investigator?.....	5
3. When must this form be completed and signed by an investigator?.....	5
4. Must the investigator be a physician?.....	5
5. What are the minimum qualifications of an investigator?.....	6
6. Does the 1572 need to be submitted to FDA?.....	6
7. When must a 1572 be updated or a new 1572 completed and signed by an investigator to reflect new or changed information?	6
8. If a clinical investigation is not conducted under an IND or is for a medical device, must investigators sign a 1572?.....	6
9. Must a sponsor conduct a foreign clinical study under an IND?.....	7
10. Must investigators who conduct studies outside of the United States sign a 1572?.....	7
11. If a foreign clinical study is being conducted under an IND, what are the investigator's responsibilities with respect to local laws and regulations?.....	7
12. For foreign clinical studies conducted under an IND, how can an investigator sign the 1572 when the investigator knows he/she cannot commit to all of the requirements on the form, specifically IRB membership. (21 CFR 56.107)?.....	7
13. If a sponsor chooses to conduct a foreign clinical study (or operate non-US sites in a multinational study) under an IND and the investigators at these non-US sites comply with the ICH E6 Good Clinical Practice Consolidated Guidance, would the non-US investigators also be in compliance with FDA's IND requirements under 21 CFR Part 312?.....	8
14. Must foreign clinical study sites in a multinational study that includes domestic sites be conducted under an IND?.....	9
15. How does a sponsor submit information to FDA about a foreign clinical study that was not conducted under an IND?.....	9
16. Should a new form be prepared and signed when the OMB expiration date is reached?.....	10
17. Does FDA expect a double-sided 1572, or is a two-page document printed from the FDA website acceptable?.....	10
18. How should the 1572 be completed.....	10
II. SECTION #1: NAME AND ADDRESS OF INVESTIGATOR	10
19. How should an investigator's name appear on the 1572?.....	10
20. What address should be entered into Section #1?.....	10
21. Should co-investigators be listed on the 1572 in Section #1? Is it acceptable to have more than one investigator at a single site?.....	10

Contains Nonbinding Recommendations

III. SECTION #2: EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY

THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION.....11

- 22. What is the purpose of Section #2?.....11
- 23. Does the CV or other statement of qualifications need to be updated during a study?.....11
- 24. Are CVs required to be signed and dated?.....11

IV. SECTION #3: NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.....11

- 25. What address(es) should be entered in Section #3?.....11
- 26. What qualifies as a research facility for Section #3?.....12
- 27. If an investigator sees study subjects at more than one site, should the investigator list all sites on the 1572?.....12

V. SECTION #4: NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.....12

- 28. What qualifies as a clinical laboratory facility for Section #4?.....12
- 29. If a laboratory is sending samples to satellite or other contract labs for additional testing, should these labs be identified in Section #4?.....12

VI. SECTION #5: NAME AND ADDRESS OF INSTITUTIONAL REVIEW BOARD (IRB) RESPONSIBLE FOR THE REVIEW AND APPROVAL OF THE STUDY(IES)

- 30. Does the IRB reviewing and approving the clinical study have to be at the same location as where the research is conducted?.....13

VII. SECTION #6: NAMES OF THE SUBINVESTIGATORS.....13 WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S)

- 31. Who should be listed as a subinvestigator in Section #6?.....13
- 32. Should research nurses, other nurses, residents, fellows, office staff, or other hospital staff be listed in Section #6?.....13
- 33. Should pharmacists or research coordinators be listed in Section #6?.....14
- 34. Is a statement of qualifications required for subinvestigators?.....14
- 35. Do individuals who are listed in Section #6 on the 1572 have to submit information about their financial interests?.....14

VIII. SECTION #7: NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR...15

- 36. What information should be included in this section?.....15

Contains Nonbinding Recommendations

IX. SECTION #8: CLINICAL PROTOCOL INFORMATION.....15

37. How should Section #8 be completed for a phase 4 study?.....15

38. Can an investigator submit the study protocol instead of an outline of the study protocol?.....15

Contains Nonbinding Recommendations

Information Sheet Guidance For Sponsors, Clinical Investigators, and IRBs⁶ Frequently Asked Questions Statement of Investigator (Form FDA 1572)

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

This guidance is intended to assist sponsors, clinical investigators, and institutional review boards (IRBs) involved in clinical investigations of investigational drugs and biologics. This guidance applies to clinical investigations conducted under 21 CFR Part 312 (Investigational New Drug Applications or IND regulations). It describes how to complete the Statement of Investigator form (Form FDA 1572).

The Food and Drug Administration (FDA or agency) has received a number of questions about Form FDA 1572. The most frequently asked questions are answered below. If you do not see your question answered here, you may submit it to gcp.questions@fda.hhs.gov or druginfo@fda.hhs.gov.

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

I. GENERAL

1. What is the Statement of Investigator, Form FDA 1572?

The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The most recent version of the 1572 is available online at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Contains Nonbinding Recommendations

2. Why does this form need to be completed by an investigator?

⁶ This guidance document was developed by the Office of Good Clinical Practice in cooperation with the Agency's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

The 1572 has two purposes: 1) to provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the clinical investigation, and 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations. Investigators should complete the form as accurately as they can. Investigators should be aware that making a willfully false statement is a criminal offense under 18 U.S.C. 1001. Further, submission of a deliberately false statement to the sponsor or to the agency can be taken into consideration in a disqualification proceeding.

3. When must this form be completed and signed by an investigator?

Whenever a sponsor selects a new investigator to participate in a clinical investigation that is being conducted under an investigational new drug application (IND), the sponsor must obtain a completed and signed 1572 before permitting the investigator to begin participation in the clinical investigation (21 CFR 312.53(c)). The investigator should sign the form only after being given enough information to be informed about the clinical investigation and to understand the commitments described in Section #9 of the 1572. Having enough information about the study typically means that the investigator has received copies of, has read, and understands the protocol and investigator's brochure (if required⁷), and is familiar with the regulations governing the conduct of clinical studies.

The investigator's signature on this form constitutes the investigator's affirmation that he or she is qualified to conduct the clinical investigation and constitutes the investigator's written commitment to abide by FDA regulations in the conduct of the clinical investigation.

4. Must the investigator be a physician?

The regulations do not require that the investigator be a physician. Sponsors are required to select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 312.53(a)). In the event the clinical investigator is a non-physician, a qualified physician (or dentist, when appropriate) should be listed as a subinvestigator for the trial and should be responsible for all trial-related medical (or dental) decisions. (ICH E6 section 4.3.1; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>).

⁷ See 21 CFR 312.55; a study initiated by a sponsor-investigator is not required to have an investigator's brochure.

5. What are the minimum qualifications of an investigator?

As stated in #4, the regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a clinical investigation. Sponsors have discretion in determining what qualifications, training, and experience will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) regulations (i.e., 21 CFR Parts 50 and 56) and practices as well as good clinical practice (GCP) regulations (see 21 CFR Part 312) and standards (e.g., ICH E6) for the conduct of clinical studies.

6. Does the 1572 need to be submitted to FDA?

No. Although the sponsor is required to collect the 1572 from the investigator, FDA does not require the form to be submitted to the agency. Many sponsors submit the 1572 to FDA, however, because it collects, in one place, information that must be submitted to FDA under 21 CFR 312.23(a)(6)(iii)(b).

7. When must a 1572 be updated or a new 1572 completed and signed by an investigator to reflect new or changed information?

There are two instances when it is necessary for an investigator to complete and sign a new 1572: when an investigator is participating in a new protocol that has been added to the IND and when a new investigator is added to the study (21 CFR 312.53(c)).

If there are other changes to information contained on a signed and dated 1572 (e.g., an IRB address change, the addition of new subinvestigators, the addition of a clinical research lab), the investigator should document the changes in the clinical study records and inform the sponsor of these changes, so that the sponsor can appropriately update the IND. The 1572 itself does not need to be revised and a new 1572 need not be completed and signed by the investigator. The sponsor can accumulate certain changes and submit this information to the IND in, for example, an information amendment or a protocol amendment.

8. If a clinical investigation is not conducted under an IND or is for a medical device, must investigators sign a 1572?

No. Under the regulations, a 1572 is only required for studies of investigational drugs and biologics conducted under an IND. It is not required for studies that are not done under an IND, and is not applicable to investigational device studies. Sponsors of device studies must obtain a signed investigator agreement (containing information similar to that requested on the 1572) from each participating investigator, per 21 CFR 812.43(c).

Contains Nonbinding Recommendations

9. Must a sponsor conduct a foreign clinical study under an IND?

No. A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived (see #12 and #13 below). When the foreign clinical study is not conducted under an IND, the sponsor must ensure that this study complies with 21 CFR 312.120, “Foreign clinical studies not conducted under an IND,” if the sponsor intends to submit the study to FDA to support clinical investigations conducted in the United States and/or marketing approval. An application based solely on foreign clinical data must meet criteria listed in 21 CFR 314.106.

10. Must investigators who conduct studies outside of the United States sign a 1572?⁸

If a foreign clinical study is conducted under an IND, then all FDA IND regulations, including the requirement to obtain a signed 1572, must be met. If a clinical study is conducted outside of the U.S. and is not conducted under an IND, then the investigator need not sign a 1572. If local laws or regulations prohibit the signing of a 1572, FDA would expect the sites to operate as non-IND sites and the study conducted as a non-IND study. If the study data is to be submitted to support a marketing application (e.g., a new drug application (NDA)), the study must be conducted in compliance with 21 CFR 312.120.

11. If a foreign clinical study is being conducted under an IND, what are the investigator’s responsibilities with respect to local laws and regulations?

Investigators are responsible for complying with the applicable laws and regulations of the country in which the study is being conducted, regardless of whether the study is being conducted under an IND. We recommend that sponsors obtain signed, written statements from investigators acknowledging their commitment to comply with local laws and requirements. In addition, if a foreign clinical study is being conducted under an IND, the investigator must sign Form FDA 1572 (investigator statement) and ensure that the study is conducted in accordance with the investigator statement and all other applicable regulations under 21 CFR Part 312.

12. For foreign clinical studies conducted under an IND, how can an investigator sign the 1572 when the investigator knows he/she cannot commit to all of the requirements on the form, specifically IRB membership (21 CFR 56.107)?

IRB review and approval is required before a clinical study can be initiated under an IND (21 CFR 56.103(a)). FDA may waive any of the IRB requirements for specific research activities or for classes of research activities otherwise covered by the IRB regulations (21 CFR 56.105), but FDA uses the waiver provision only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable. The most common circumstance for which FDA receives a waiver request is when a sponsor wishes to conduct a foreign clinical study under an IND. In this case, typically an Independent Ethics Committee (IEC) that operates in accordance with Good Clinical

Contains Nonbinding Recommendations

⁸ Investigators conducting studies outside of the U.S. may want to consult with local regulatory authorities for additional guidance when considering whether to conduct studies under an IND.

Practice (GCP) is utilized instead of a U.S. IRB. Although its membership and functions for assuring human subject protection are comparable to an IRB, an IEC may not meet all of the IRB requirements contained in 21 CFR Part 56.

For a foreign study, an IRB waiver request should contain a description of alternative mechanisms for assuring human subject protection. It would generally be acceptable for a waiver request to state the intention to use an IEC that complies with GCP (e.g., ICH E6) instead of an IRB that complies with 21 CFR Part 56.

The sponsor should submit the waiver request to the IND under which the study will be conducted. The IND will have been submitted to the appropriate review division in either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The sponsor will be informed by the agency in writing whether the waiver request is denied or granted. If a waiver is granted, the sponsor should have investigators attach a copy of the letter granting the waiver to the signed 1572 in the investigator's record.

13. If a sponsor chooses to conduct a foreign clinical study (or operate non-US sites in a multinational study) under an IND and the investigators at these non-US sites comply with the ICH E6 Good Clinical Practice Consolidated Guidance, would the non-US investigators also be in compliance with FDA's IND requirements under 21 CFR Part 312?

Yes, with two exceptions. The first is that the FDA requirements for IRBs under 21 CFR Part 56 are slightly different with respect to membership and function. To address this issue, as described in #12 above, FDA can provide a specific waiver from the Part 56 IRB requirements, allowing an IEC that complies with good clinical practice to substitute for the IRB.⁹ The second exception is that the requirements for informed consent under 21 CFR Part 50 for particular clinical trials (e.g., emergency research under 21 CFR 50.24, clinical investigations involving pediatric subjects under Subpart D) are more extensive with respect to IRB responsibilities. Because these types of trials are uncommon, our experience has not revealed that this has caused a conflict; but in the event of one, we would be willing to discuss a resolution with the sponsor on a case-by-case basis. If the investigator or sponsor believes that there are other conflicting requirements, the sponsor may request a waiver from FDA from the specific requirement under 21 CFR 312.10.

Contains Nonbinding Recommendations

⁹ See "Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Waiver of IRB Requirements for Drug and Biological Product Studies," January 2006, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080613.pdf>.

14. Must foreign clinical study sites in a multinational study that includes domestic sites be conducted under an IND?

No. A multinational study may include domestic sites under the IND and foreign sites not under the IND. Investigational drug and biologics studies conducted in the U.S. must be conducted in compliance with the IND requirements contained in 21 CFR 312, which includes the requirement that investigators sign the 1572. If a study also involves foreign clinical sites, the sponsor may choose, but is not required, to include the foreign clinical sites under the IND. The investigators from the U.S. sites and any foreign sites included under the IND would be required to sign the 1572. The investigators from the foreign sites that are not included under the IND are not required to sign the 1572.

If the sponsor chooses to conduct a multinational study with U.S. and some foreign sites under the IND, and other foreign sites not under the IND, the sponsor can submit a single protocol to the IND and all sites would follow this protocol. Alternatively, the sponsor can conduct a multinational study with one protocol for sites under the IND (U.S. sites and some foreign sites) and a different protocol(s) for foreign sites not under the IND. If the intent is to pool the data from U.S. and foreign sites, the protocols would ordinarily be very similar or identical. The U.S. sites and any foreign sites included under the IND must follow the protocol that was submitted to the IND. For foreign sites that are not included under the IND, the protocol(s) does not need to be submitted to the IND. In general, if the sponsor intends to submit the data in an application for marketing approval, we recommend that the sponsor identify the foreign sites that will not be conducted under the IND and discuss plans to pool the data from U.S. and foreign sites with the appropriate FDA review division.

Note, however, that 21 CFR 312.32(b) requires sponsors to promptly review information about the safety of the investigational drug obtained or otherwise received by the sponsor from any source, foreign or domestic. Under 21 CFR 312.32(c), sponsors must also notify FDA and all participating investigators in an IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. This means that FDA and all participating investigators under the IND would be informed of such an adverse experience, even if it occurred in a foreign study not conducted under the IND.

15. How does a sponsor submit information to FDA about a foreign clinical study that was not conducted under an IND?

Under 21 CFR 312.120, the sponsor can submit information to FDA from a foreign clinical study that was not conducted under an IND to support clinical investigations in the United States and/or marketing approval. When submitting information about a foreign clinical study, it is helpful to clearly identify in the cover letter that the material is being submitted in accordance with 21 CFR 312.120. The submission requirements for supporting documentation can be found at 21 CFR 312.120(b).

Contains Nonbinding Recommendations

16. Should a new form be prepared and signed when the OMB expiration date is reached?

No. There is no need to prepare and sign a new 1572 when the OMB expiration date has been reached.

17. Does FDA expect a double-sided 1572, or is a two-page document printed from the FDA website acceptable?

Either is acceptable; however, FDA recommends that a two-page document be stapled so that there is no question about what form the investigator signed.

18. How should the 1572 be completed?

The 1572 on FDA's website may be completed by typing the information directly into the fillable form and printing the completed form. Alternatively, it is acceptable to print the blank form from FDA's website and hand-write or type the information onto the form. Typed forms are preferable because they are usually more legible. The completed form must be signed and dated by the investigator (either by hand or using an acceptable electronic method).

II. SECTION #1: NAME AND ADDRESS OF INVESTIGATOR

19. How should an investigator's name appear on the 1572?

Section #1 should contain the investigator's full legal name (e.g., name on the investigator's birth certificate or marriage certificate). Titles, degrees, and/or professional qualifications may follow the investigator's legal name, if desired.

20. What address should be entered into Section #1?

The address where the investigator can be reached by mail or in person should be entered in Section #1 of the 1572. Usually, this corresponds to the investigator's work or business address.

21. Should co-investigators be listed on the 1572 in Section #1? Is it acceptable to have more than one investigator at a single site?

The term co-investigator is not defined in FDA regulations. As commonly used, the term is meant to indicate that each co-investigator is fully responsible for fulfilling all of the obligations of an investigator as identified in 21 CFR 312.60. Thus under 21 CFR 312.3(b), each co-investigator is an investigator, and as such must sign a separate 1572.

In some situations, it is preferable to have more than one investigator responsible for a clinical investigation. For example, when a study is conducted at multiple research facilities that are not in close proximity, FDA expects an investigator who has signed a

Contains Nonbinding Recommendations

1572 to be available at each location to either personally conduct or supervise the study. This responsibility cannot be delegated to a subinvestigator.

Although not necessary, it is acceptable to have more than one investigator at a single site. For example, the conduct and supervision of a large investigation with many subjects or complicated procedures might be shared among several investigators, each of whom has signed a 1572 when the investigation is conducted under an IND. This is distinct from a subinvestigator (see #31) whose role in the clinical investigation is more limited.

III. SECTION #2: EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION

22. What is the purpose of Section #2?

Section #2 requires the investigator to attach a curriculum vitae (CV) or other statement of qualifications, showing the education, training and experience that qualifies the investigator as an expert in the clinical investigation of the drug/biologic for the use under investigation. Information identified in this section and attached to the 1572 enables the sponsor to assess an investigator's qualifications.

23. Does the CV or other statement of qualifications need to be updated during a clinical study?

No. FDA regulations do not require a CV or other statement of qualifications to be updated during a clinical study.

24. Are CVs required to be signed and dated?

No. FDA regulations do not require a CV to be signed and dated. The investigator's dated signature on the 1572 is sufficient to attest to the accuracy of the CV or other statement of qualifications submitted with the 1572.

IV. SECTION #3: NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED

25. What address(es) should be entered in Section #3?

The address(es) of the location(s) where the investigation will be conducted and to where the test articles will be shipped, if different from the investigator's address of record, should be entered in Section #3.

Contains Nonbinding Recommendations

26. What qualifies as a research facility for Section #3?

Section #3 is intended to identify facilities where study activities will be conducted and clinical data will be generated or collected. This includes facilities where subjects will be seen and study procedures performed. For example, this might include locations such as health care facilities where the test article will be administered, or where physical exams will be performed. Facilities where other important clinical investigation functions are performed may also be identified in Section #3. For example, a research laboratory where the test article is prepared, a special storage facility where the test article will be kept, or a location where tissue specimens are collected should be listed in this section.

27. If an investigator sees study subjects at more than one site, should the investigator list all sites on the 1572?

Yes. The names and addresses of each of the study sites should be identified in Section #3. However, if the protocol specifies that the investigative product can be administered at a subject's home (for example, the protocol allows for daily injections to be administered by a registered nurse in the subject's home), the subjects' home addresses do not have to be listed on the 1572. Study records should reflect that the test article was administered at subjects' homes per the protocol.

V. SECTION #4: NAME AND ADDRESS OF CLINICAL LABORATORY FACILITIES TO BE USED IN THIS STUDY

28. What qualifies as a clinical laboratory facility for Section #4?

Section #4 is intended to identify clinical laboratories or testing facilities directly contributing to or supporting the clinical study (for example, diagnostic labs performing blood work, imaging centers, cardiology labs, etc.). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data for clinical investigations conducted under an IND.

29. If a laboratory is sending samples to satellite or other contract labs for additional testing, should these labs be identified in Section #4?

It is only necessary to list the primary laboratory, provided that laboratory can trace the samples to each of the satellite and/or contract labs where the tests were performed.

VI. SECTION #5: NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) RESPONSIBLE FOR THE REVIEW AND APPROVAL OF THE STUDY(IES)

Contains Nonbinding Recommendations

30. Does the IRB reviewing and approving the clinical study have to be at the same location as where the research is conducted?

The regulations permit review of research by IRBs at locations other than where the research is being performed (e.g. independent or non-institutional IRB; use of a cooperative IRB review process; see 21 CFR 56.114). Therefore an IRB may review clinical studies that are not performed on-site as long as requirements in 21 CFR Parts 50 and 56 are met. For more information on cooperative research arrangements, see the FDA Guidance for Industry-Using a Centralized IRB Review Process in Multicenter Clinical Trials (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm>).

VII. SECTION #6: NAMES OF THE SUBINVESTIGATORS WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S)

31. Who should be listed as a subinvestigator in Section #6?

FDA's regulation at 21 CFR 312.3(b) states: "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." 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "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)."

The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant clinical investigation-related duties). In general, if an individual is directly involved in the performance of procedures required by the protocol, and the collection of data, that person should be listed on the 1572. For example, if the protocol notes that each subject needs to visit a specified internist who will perform a full physical to qualify subjects for the clinical investigation, that internist should be listed in Section #6.

32. Should research nurses, other nurses, residents, fellows, office staff, or other hospital staff be listed in Section #6?

Hospital staff, including nurses, residents, or fellows and office staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the clinical data, do not need to be listed individually. It is not necessary to include in this section a person with only an occasional role in the conduct of the research, e.g., an on-call physician who temporarily dealt with a possible adverse effect or a temporary substitute for any research staff (see ICH E3, Section 6) (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073113.pdf>).

Contains Nonbinding Recommendations

Concerning staff residents on rotation, it may be difficult to prospectively identify those individuals who might perform specified protocol procedures or collect clinical data. Specific names of the rotational staff do not have to be listed in Section #6. Instead, to successfully address this scenario, the names of rotational individuals and the procedures they are expected to perform should be included in the clinical study records. This information should also be sent to the sponsor for submission to FDA in, for example, an information amendment.

33. Should pharmacists or research coordinators be listed in Section #6?

The decision about whether to list a pharmacist or research coordinator on the 1572 is a matter of judgment, dependent upon the contribution that the individual makes to the study. For example, a research pharmacist may prepare test articles and maintain drug accountability for many clinical studies that are ongoing concurrently at an institution. Because the pharmacist would not be making a direct and significant contribution to the data for a particular study, it would not be necessary to list the pharmacist as a subinvestigator in Section #6, but he/she should be listed in the investigator's study records.

Generally, a research coordinator has a greater role in performing critical study functions and making direct and significant contributions to the data. For example, a research coordinator often recruits subjects, collects and evaluates study data, and maintains study records. Therefore, the research coordinator should usually be listed in Section #6 of the 1572.

34. Is a statement of qualifications required for subinvestigators?

No. The regulations at 21 CFR 312.53(c)(1)(viii) require only that subinvestigators' names be listed in Section #6 of the 1572. It is the responsibility of the sponsor to select investigators qualified by training and experience, as appropriate experts, to investigate the drug. The investigator must ensure that all associates, colleagues, and employees assisting with the conduct of the clinical investigation are aware of their obligations including complying with the IND regulations.

35. Do individuals who are listed in Section #6 on the 1572 have to submit information about their financial interests?

Yes. Under 21 CFR Part 54 (Disclosure of Financial Interests by Clinical Investigators), a person listed or identified as an investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects must submit financial disclosure information to the sponsor. For purposes of this financial disclosure regulation, the term investigator also includes the spouse and each dependent child of the investigator and subinvestigator. (21 CFR 54.2(d) and 54.4). For additional information about financial disclosure, see FDA's Guidance for Industry Financial Disclosure by Clinical Investigators (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm>)

Contains Nonbinding Recommendations

VIII. SECTION #7: NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

36. What information should be included in this section?

List the name and code number (if any) of all the protocols under the IND that will be conducted by the investigator signing the 1572. A code number is an identifying number assigned by the sponsor. As a reminder, some investigators may be responsible for submitting certain clinical trial information to the National Institutes of Health clinical trials data bank under 42 U.S.C. 282(j), 402(j) of the Public Health Service Act. Although not all investigators will be expected to meet this requirement, go to www.clinicaltrials.gov for further information about potential responsibilities.

IX. SECTION #8: CLINICAL PROTOCOL INFORMATION

37. How should Section #8 be completed for a phase 4 study?

Phase 4 refers to the timing of a clinical study (i.e., postmarketing) rather than the characteristics of the study, which are described under 21 CFR 312.21, Phases of an investigation. A postmarketing clinical trial would meet the description of a phase 2 or 3 investigation and a full protocol would be submitted. The investigator does not need to mark either of the boxes in Section #8, but should identify in Section #7 that the study is a phase 4 study.

38. Can an investigator submit the study protocol instead of an outline of the study protocol?

Yes. The protocol or a detailed description is required for any phase 2 or 3 clinical trial. Phase 1 studies can be supported by an outline (see 21 CFR 312.53).

Appendix 8: FDA Draft Guidance for industry and FDA Administration Staff – Investigational Device Exemptions (IDE) for Early Feasibility Medical device Clinical Studies, Including Certain First in Human (FIH) Studies

Draft Guidance for Industry and Food and Drug Administration Staff - Investigational Device Exemptions (IDE) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

¹DRAFT GUIDANCE

**This guidance document is being distributed for comment purposes only.
Document issued on: November 10, 2011**

You should submit comments and suggestions regarding this draft document within **90** days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>². Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Andrew Farb, 301-769-6343, Andrew.Farb@fda.hhs.gov or Dorothy Abel, 301-796-6366, Dorothy.Abel@fda.hhs.gov.



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

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number 1782 to identify the guidance you are requesting.

Table of Contents

- [1. Introduction](#)
- [2. Overview](#)
- [3. Regulatory Background](#)

[Click Here to Go to the Table of Contents](#)

- 4. Targeting Approval for an Early Feasibility Study IDE Application
- 5. Report of Prior Investigations
 - 5.1. Design concept
 - 5.2. Device evaluation strategy
 - 5.2.1. Device evaluation strategy for the early feasibility study
 - 5.2.2. Overall device evaluation strategy (optional)
 - 5.3. Bench and laboratory testing and computational modeling
 - 5.4. In vivo animal studies
 - 5.5. Prior clinical information
- 6. Investigational Plan
 - 6.1. Risk analysis and mitigation
 - 6.2. Clinical protocol
 - 6.3. Human subject protection measures
 - 6.3.1. Informed consent
 - 6.3.2. Institutional Review Board
 - 6.4. Monitoring
 - 6.4.1. Monitoring procedures
 - 6.4.2. Data monitoring committee (DMC)
- 7. Iterations During Early Feasibility Studies
 - 7.1. Changes requiring FDA notification (5-day notice)
 - 7.2. Changes requiring FDA approval
- 8. Next Steps in Clinical Evaluation
- 9. Conclusions
- Appendix 1: Device Evaluation Strategy Example
- Appendix 2: Device iteration example

**Draft Guidance for Industry and Food and Drug Administration Staff
Early Feasibility Medical Device Clinical Studies, Including Certain First in
Human (FIH) Studies**

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

1. Introduction

This document is intended to provide guidance to FDA staff, clinicians, clinical innovators, and industry on the development and review of Investigational Device Exemption (IDE) applications for early feasibility studies of significant risk devices.¹ Early feasibility studies allow for early clinical evaluation of devices to provide proof of principle and initial clinical safety data. These studies may be appropriate early in device development when clinical experience is necessary because nonclinical testing methods are not available or adequate to provide the information needed to advance the developmental process. However, as with all clinical studies, initiation of

an early feasibility study must be justified by an appropriate risk-benefit analysis and adequate human subject protection measures.

For the purposes of this guidance, clinical study types are defined as follows:

- An **early feasibility study** is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication (e.g., innovative device for a new or established intended use, marketed device for a novel clinical application). It may be used to evaluate the device design concept with respect to basic safety and device functionality in a small number of subjects (generally fewer than 10 initial subjects) when this information cannot be readily provided through additional nonclinical assessments or appropriate nonclinical tests are unavailable. Information obtained from an early feasibility study may guide device modifications. An early feasibility study does not necessarily involve the first clinical use of a device.
- A **first in human (FIH) study** is a type of study in which a device for a specific indication is evaluated for the first time in human subjects. This document only discusses FIH studies that meet the definition of an early feasibility study.
- A **traditional feasibility study** is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study. As compared to an early feasibility study, more nonclinical (or prior clinical) data are necessary for approval to initiate a traditional feasibility study²; however, a traditional feasibility study does not necessarily need to be preceded by an early feasibility study.
- A **pivotal study** is a clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects. It may or may not be preceded by an early and/or a traditional feasibility study.

Early feasibility studies may be conducted for multiple reasons, such as obtaining *initial* insights into:

- the safety of the device-specific aspects of the procedure;
- whether the device can be successfully delivered, implanted or used;
- operator technique challenges with device use;
- human factors (e.g., difficulties in comprehending procedural steps);
- the safety of the device (e.g., evaluation of device-related serious adverse events);
- whether the device performs its intended purpose (e.g., mechanical function, making intended measurements);
- device failures;
- patient characteristics that may impact device performance (e.g., anatomical limitations); and
- therapeutic parameters (e.g., energy applied, sizing, dose released) associated with device use.

Early feasibility studies are not designed or intended to generate definitive data to independently support a marketing application in lieu of a pivotal clinical trial. Further, unlike traditional feasibility studies, which are focused on providing initial safety and effectiveness information for

a near final or final device design or capturing data to guide the development of a pivotal study, early feasibility studies have a broader purpose. Early clinical experience obtained from an early feasibility study increases the efficiency of the device development process, as it may be used to:

- identify appropriate modifications to the procedure or device;
- optimize operator technique;
- refine the intended use population;
- refine non-clinical test plans or methodologies; and
- develop subsequent clinical study protocols.

To determine which type of clinical study (early feasibility, traditional feasibility, or pivotal) is appropriate to pursue, certain factors, such as the novelty of the device, its intended clinical use, the stability of the device design, and the amount of test data available to support the IDE application should be considered. An early feasibility study is appropriate when device changes are expected and when, due to the novelty of the device or its intended use, a clinical study is expected to provide information that cannot be readily provided through additional nonclinical assessments. An early feasibility study may be appropriate even if a device or a prototype of the device has previously been used clinically for the intended clinical use. Please note that not all novel devices or uses warrant an early feasibility study. Either a traditional feasibility study or a pivotal study may be more appropriate if the device design is near-final or final, respectively, depending on the amount of data available to justify the study. Prior to IDE submission and to avoid preventable delays, it is advisable to contact FDA to determine whether the proposed investigation can be classified as an early feasibility study.

The guidance provided herein is specific to early feasibility study IDEs only and is not applicable to other types of clinical studies. As discussed above, excluded from the scope of this document are studies involving the first human use of a device that does not otherwise meet the definition of an early feasibility study. For example, the first human use of a non-innovative device for a well-understood clinical use could appropriately be evaluated under a traditional feasibility or a pivotal study rather than an early feasibility study.

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

2. Overview

FDA recognizes the value of encouraging medical device innovation to address clinical needs and improve patient care, particularly when alternative treatments or assessments are unavailable, ineffective, or associated with substantial risks to patient safety. This guidance has been developed to facilitate the early clinical evaluation of medical devices in the United States under the IDE regulations, using risk mitigation strategies that appropriately protect human subjects in early feasibility studies.

An early feasibility study IDE application must comply with section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 360j(g)] and 21 CFR Part 812; however, the [Click Here to Go to the Table of Contents](#)

procedures and conditions prescribed for IDEs may vary depending on the type of clinical study (see Section 3).

This guidance outlines new policy regarding the application for and approval of early feasibility study IDEs. The essential elements of this policy are:

1. FDA approval of an IDE application for an early feasibility study, including certain first in human studies, may be based on less nonclinical data than would be expected for a traditional feasibility or a pivotal study (see Section 4). This is because early feasibility studies are only appropriate where additional nonclinical testing is not available or adequate to provide the information needed to advance the developmental process. Identification of the data necessary to support an early feasibility study should be based on a thorough device evaluation strategy that describes the device and procedure-related attributes and addresses the potential failure modes (see Section 5.2.1). This policy is intended to facilitate initiation of clinical studies in the United States earlier in the device development process than has historically occurred, when appropriate.³
2. This guidance introduces new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study while still requiring compliance with the IDE regulations in 21 CFR Part 812 (see Section 7), as follows:
 - more types of modifications that can be made under a 5 day notification without prior FDA approval as compared with other types of studies;
 - a contingent approval process that permits changes contingent upon acceptable nonclinical test results without requiring additional FDA action;
 - interactive review of IDE supplements.

This guidance document highlights and reviews key principles unique to an early feasibility study IDE with respect to the Report of Prior Investigations, the clinical protocol, risk mitigation strategies, and subject protection measures (see Sections 5 and 6). This guidance is not intended to address all required elements of IDE applications, generally, or to provide a comprehensive tutorial on best clinical practices for investigational medical device studies. Furthermore, while this document outlines the general principles for preparing and reviewing early feasibility study IDE applications, it is not intended to provide guidance on the device-specific nonclinical information needed to justify initiation of an early feasibility study, or the specific data required to progress to other phases of clinical study for a particular device type or clinical indication. Pre-submission discussions with FDA are necessary to optimize the preparation and quality of early feasibility study IDE applications.

3. Regulatory background

Section 520(g) of the FD&C Act establishes a framework for FDA to grant devices for investigational use an exemption from certain requirements so that experts qualified by scientific training and experience can investigate their safety and effectiveness. This exemption is known as an Investigational Device Exemption (IDE). For significant risk devices, the sponsor must first submit an IDE application and obtain FDA approval.⁴

The FD&C Act expressly recognizes that information to be included in an IDE application may vary depending on the investigation. Section 520(g)(2)(C) states:

Procedures and conditions prescribed [for granting investigational device exemptions] may appropriately vary depending on

- the scope and duration of clinical testing to be conducted under such exemption,
- the number of human subjects that are to be involved in such testing,
- the need to permit changes to be made in the device subject to the exemption during testing conducted in accordance with a clinical testing plan required under paragraph (3)(A), and
- whether the clinical testing of such device is for the purpose of developing data to obtain approval for the commercial distribution of the device.

As with all clinical studies of investigational devices, an early feasibility study must comply with 21 CFR Part 812, including the requirements outlined below:

- Application (21 CFR 812.20): explains when a sponsor must submit an IDE application and the information that the IDE application must contain, including the investigational plan and report of prior investigations.
- Investigational Plan (21 CFR 812.25): explains what information the Investigational Plan must contain, including the purpose of the investigation, the protocol, risk analysis, description of the device, monitoring procedures, labeling, consent materials, and information about the Institutional Review Boards (IRB) reviewing the investigation.
- Report of Prior Investigations (21 CFR 812.27): explains what information the Report of Prior Investigations must contain, including reports of all prior clinical, animal, and laboratory testing of the device.
- Supplemental applications (21 CFR 812.35): explains when changes to the device and Investigational Plan must have prior FDA approval and the appropriate manner to notify FDA of changes that do not require prior approval.

Adopting the principles set forth in section 520(g)(2)(C) of the FD&C Act, Sections 4-7 of this guidance clarify how some of these requirements should be applied to early feasibility study IDEs.

4. Targeting approval for an Early Feasibility Study IDE Application

Because there are differences in the amount and type of information that is needed for an early feasibility study IDE application as compared to a traditional feasibility or pivotal study IDE application, the IDE application should clearly state that the proposed study is an early feasibility study and provide justification for conducting this type of study. To improve the likelihood of IDE approval, the following questions should be addressed by the sponsor, with supporting materials, in the original early feasibility study IDE application:

1. What is the clinical condition to be treated or assessed by the device?
2. What is the standard of care for the clinical condition and expected clinical outcomes associated with the standard of care?
3. Does the information included in the Report of Prior Investigations (Section 5) support initiation of the study?

4. Does the Investigational Plan include a thorough risk/benefit analysis, sufficient risk mitigation strategies, adequate human subject protection measures, and an appropriate clinical study protocol (see Section 6)?
5. Is initiation of the clinical study justified based on the responses to the aforementioned questions?

Under 21 CFR 812.30(a), FDA may approve an investigation as proposed, approve it with conditions, or disapprove it. FDA may disapprove an IDE application if it finds that any of the grounds in 21 CFR 812.30(b) exist. The ground for disapproval provided at 21 CFR 812.30(b)(4) is of particular importance for early feasibility studies:

- 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.

Early feasibility studies are designed to gain initial clinical insights and not data to independently support a marketing application. They may be initiated based on less evidence than for other types of clinical studies and before the design of the device is finalized because they are only appropriate where additional nonclinical testing is not available or adequate to provide the information needed to advance device development. As a result, early feasibility studies may carry greater unknown risk than traditional feasibility and pivotal studies. This makes human subject protection measures, such as adequate informed consent and IRB review, all the more important in an early feasibility study (see Section 6). At the same time, benefits deriving from the knowledge to be gained may be substantial, particularly for innovative devices or intended uses during the early phase of device development. Even though early feasibility studies are not designed or intended to generate statistically valid results, they should be scientifically sound (e.g., enrolling the right subjects and utilizing meaningful endpoints) so that the results can be used to further device development. Importantly, as early feasibility studies can begin before the design of the device is finalized, there still should be reason to believe that the device will be effective.

Compared to a traditional feasibility or pivotal study, less nonclinical data would generally need to be included in the Report of Prior Investigations for an early feasibility study IDE application. For example, nonclinical testing using small sample sizes or short implant durations for *in vivo* animal studies may be sufficient to justify initiation of an early feasibility study. Under this approach, if additional and longer-term bench and animal testing are needed prior to permitting a larger clinical study of a near-final or final device design, these tests could be completed concurrently with the early feasibility study.

Some essential elements of a pivotal study, such as a prospective definition of study success and a prespecified data analysis plan, are not necessary for early feasibility study IDE applications. In addition, an early feasibility study protocol may be subject to fewer constraints as compared to a pivotal study protocol. For example, for early feasibility studies, sequential enrollment typically would not be necessary, and documentation in case report forms might be limited to highly relevant data fields.

5. Report of Prior Investigations

[Click Here to Go to the Table of Contents](#)

The requirements in 21 CFR 812.27 apply to the Report of Prior Investigations for early feasibility study IDE applications. The information in this section is intended to clarify how certain of these requirements apply to early feasibility studies.

The Report of Prior Investigations must include the information needed to justify a clinical investigation of a device.⁵ For early feasibility studies, this information should:

- support an expectation of acceptable clinical use (e.g., successful device placement using a benchtop model that simulates clinical conditions and/or a suitable animal model) and that the device will function as intended;
- address basic device safety, including, but not limited to, sterility, biocompatibility, electromagnetic compatibility, chemical compatibility (e.g., with concomitant drugs, chemicals, cleaners); and
- characterize catastrophic failure modes and risk mitigation approaches.

When adequately justified, the information may be generated from tests utilizing non-standardized methodologies (e.g., evaluating fatigue properties using loading conditions different from those specified in a guidance document or voluntary standard or using less sensitive testing equipment than specified in a guidance or standard). In determining the testing needed, the sponsor should consider the clinical significance of potential failures and the ability to predict clinical performance based on nonclinical testing. A sponsor may be able to justify deferral of certain testing until later stages of device development.

The Report of Prior Investigations for an early feasibility study IDE application should include three main sections: (1) background, (2) an executive summary, and (3) detailed reports.

(1) The background section should describe:

- the clinical context for which the testing is being conducted:
 - the clinical condition the device is intended to treat or assess and the current standard of care; and
 - the rationale for exposing the target population to potential risks (e.g., description of the types and severity of risks posed by current treatment or assessment options and scientific data to support potential benefits);
- the design concept;
- the device evaluation strategy for the early feasibility study; and
- the rationale for providing less nonclinical testing than would be needed to support initiation of a larger clinical study.

(2) The executive summary should include:

- a description of the nonclinical testing that has been performed and relevant clinical information;
- a table describing the purpose of each test or analysis, acceptance criteria (if available), test results, and any potential clinical significance of the results.

(3) Individual test reports should be provided for each bench and laboratory test, computer modeling analysis (e.g., finite element analysis), and *in vivo* animal study. Each test report

[Click Here to Go to the Table of Contents](#)

should include the purpose, test method, sample selection, results, discussion of the acceptability of the results, and when appropriate, justification and clinical applicability of the acceptance criteria.⁶ A summary of any relevant clinical information, with references, if available, should also be provided.

5.1. Design concept

Identification of appropriate testing and test methodologies should be based on the device design concept. An early feasibility study IDE application should include information to clearly describe the design concept, such as:

- Device description (e.g., physical description, figures, materials of construction, software documentation)
- Intended function
- Intended patient population
 - Intended clinical use, designated by the medical condition or lesion type to be treated or assessed
 - Anatomical location and limitations
- Conditions of use/intended *in vivo* environment
- Directions for use
- How the intended function is achieved (i.e., key design features for the mechanism of action)
- Minimum design-life of the device.

This information is needed to guide the device evaluation strategy.

5.2. Device evaluation strategy

The device evaluation strategy in the Report of Prior Investigations is intended to describe and justify the appropriate testing to support initiation of the clinical study. The guidance below describes one appropriate method for presenting the device evaluation strategy for an early feasibility study as well as an option for obtaining early FDA feedback on the overall device evaluation strategy beyond the early feasibility phase.

5.2.1. Device evaluation strategy for the early feasibility study

The device evaluation strategy for the early feasibility study should be based on an appropriate risk assessment.⁷ In some cases, the appropriate testing to evaluate a device for use in an early feasibility study may not be found in an FDA guidance or a voluntary standard. In general, for an early feasibility study, the evaluation strategy should be focused on identifying the information needed to address significant safety concerns and support basic device functionality.

The device evaluation strategy is best outlined in a table with column headings as presented and explained below. To complete the table, the sponsor starts with listing the necessary attributes for the device (Column Number 1). Next, for each attribute, the sponsor should list the types of problems or failures that might result if the device does not function properly (Column Number 2). The specific effects of the failure modes can be device-related or clinical, and should be listed

separately (Column Numbers 3 and 4). The identified failure modes and effects of failure guide the information the sponsor needs to assess each device function (Column Number 5).

Device Evaluation Strategy Table Headings and Explanations:

Column Heading	Explanation	Context
Column 1: Device/Procedure Related Attribute	The intended or defined performance of the product.	
Column 2: Potential Failure Modes	Difficulties or failures that might be encountered that could result in consequences (effects) to the patient or device.	If the device does not have an adequate [column 1], there could be a problem with [column 2].
Column 3: Potential Effect(s) of Failure (Device)	The initial effect(s) of the failure mode on the device.	If there is a problem with [column 2], [column 3 or 4] could occur and should be documented.
Column 4: Potential Effect(s) of Failure (Clinical)	The effect(s) of the failure mode on the patient.	If there is a problem with [column 2], [column 3 or 4] could occur and should be documented.
Column 5: Information/Data	A list of information/data (e.g., bench, laboratory, analytical, animal) that should be obtained to evaluate the individual device attribute.	To evaluate the adequacy of the device's [column 1] the following information should be obtained: [column 5].

When identifying the appropriate testing to evaluate basic safety, it is necessary to consider the potential frequency, severity, and nature of the clinical effects of failure that may be associated with the device or procedure. For an early feasibility study, the focus of testing should be on identifying and minimizing the potential for adverse events associated with basic safety risks (e.g., non-biocompatibility, incompatibility between components, and catastrophic failures). With respect to device functionality, the device evaluation strategy should indicate those attributes most relevant for the intended use and appropriate testing to evaluate those attributes. For highly innovative devices, FDA recognizes that appropriate nonclinical test methodologies to assess some critical parameters may not be available, and therefore, these would need to be evaluated clinically.

The device evaluation strategy should be updated as new information emerges about the potential risks and the appropriate and necessary assessment of the device.

The following table is an example of a portion of an acceptable device evaluation strategy for a permanently implanted metallic device.

Table 1: Device Evaluation Strategy Example

Device/Procedure Related Attribute	Potential Failure Modes	Potential Effects of Failure		Information/Data
		Device	Clinical	
Implant integrity	Structural failure of implant	<ul style="list-style-type: none"> • Metallic fracture 	<ul style="list-style-type: none"> • Exacerbation of treated problem • Foreign body embolization • Trauma to adjacent structures 	<ul style="list-style-type: none"> • Discussion on design concept to optimize integrity • Comparison of design to marketed devices • Strength testing • Stress/strain analysis
	Corrosion	<ul style="list-style-type: none"> • Metallic fracture 	<ul style="list-style-type: none"> • Exacerbation of treated problem • Foreign body embolization • Trauma to adjacent structures 	<ul style="list-style-type: none"> • Comparison of materials to the sponsor's own marketed devices
Appropriate biological response	Loss of device function	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • Necrosis 	<ul style="list-style-type: none"> • Comparison of design and materials to marketed devices • Acute and medium-term implantation in an appropriate animal model

This example presumes that, based on the device design and intended use, failure due to a loss of implant integrity is unlikely to lead to serious adverse clinical effects of failure (i.e., that it would be a non-catastrophic failure), so only basic information is needed regarding structural integrity and corrosion. An appropriate biological response is a basic safety requirement, and although comparison of the design and materials to marketed devices provides useful supportive information, implantation in an animal model is needed to adequately assess this critical attribute. For both attributes in this example, less information/data is necessary than for a pivotal study.

5.2.2. Overall device evaluation strategy (optional)

Though not required for IDE approval, it may be valuable to submit a pre-IDE to obtain FDA feedback on the overall device development plan by identifying the types of information or levels of testing that may be needed to progress beyond the early feasibility study.

In the device evaluation strategy table described above, subheadings may be included under the Information/Data column, as presented in Table 2, to describe the additional information/data for each device/procedure-related function needed to support:

- initiation of a traditional feasibility study;
- initiation of a pivotal study; and
- a marketing application.

Table 2: Overall Device Evaluation Strategy

Device/Procedure Related Attribute	Potential Failure Modes	Potential Effects of Failure		Information/Data			
		Device	Clinical	Early Feasibility/FIH	Traditional Feasibility*	Pivotal	Marketing

* It may not be necessary to conduct a traditional feasibility study following an early feasibility study.

An example of an overall device evaluation strategy can be found in Appendix 1.

5.3. Bench and laboratory testing and computational modeling

For early feasibility studies, the full battery of tests that would be expected for evaluation of a final device design are not required for IDE approval. As outlined in Section 5.2, FDA encourages sponsors to consider the relationship between an attribute or device failure mode and its anticipated clinical consequences to determine the testing needed to support the IDE application. This approach may be used when justifying the device evaluation strategy, including the use of preliminary results or deferral of certain testing at the early feasibility phase of device development.

Computational modeling (CM) can be used for a variety of purposes to support the initiation of an early feasibility study. For example:

- For chronic implants in which the boundary and loading conditions are known, CM may be used to predict the long-term durability of the device.
- For chronic implants in which the boundary and loading conditions are not well-defined, CM may be useful for iterative design modifications, where simulations can be used to optimize the device design or enhance the design of prototypes.
- For certain test scenarios, which cannot be evaluated using other nonclinical methods or clinically, CM may be used. For example, to aid in assessing MRI safety, CM may be used to simulate certain worst-case MRI conditions that cannot be replicated in an animal model and cannot be tested ethically in humans.

Discussions with FDA regarding protocols for complex and novel testing are strongly encouraged.

5.4. In vivo animal studies

In vivo animal studies provide unique anatomic and clinical pathologic information on the local and systemic responses to device use. An animal study may be conducted to support the initiation of an early feasibility study when an animal model is needed to further assess basic safety or device functionality beyond the information provided from non-animal testing.

An animal study should involve the use of a validated animal model, when available, for which the results are likely to predict risks in humans. In cases in which a validated animal model is unavailable, a focused animal study to address a limited range of safety issues may be conducted to complement the non-animal testing. A rationale for addressing questions typically answered by animal studies with alternative methods or data should be provided in the IDE application.

Animal studies should not be viewed as an alternative to adequate bench testing, and whenever possible, protocols should apply the principles of reduce, replace, and refine. The size of the animal study depends on the device and assay (i.e., how well the animal model provides anatomic, physiologic, and procedural similarities to humans). Recognizing the inherent variability of results, animal studies should be large enough to show consistent results. Short-term animal studies may be adequate for the initiation of an early feasibility study. However, additional animal study data may be needed to support a larger clinical study with a near-final or final device design.

In vivo animal studies to evaluate medical devices are generally required to follow Good Laboratory Practices (GLP) for animal care and study conduct as specified in 21 CFR Part 58. However, non-GLP study data may be used to support an early feasibility study IDE application if the deviations from GLP are identified and justified and do not compromise the validity of the study results. For example, if an independent quality assurance unit is not utilized, a sponsor should describe how bias was mitigated and how the study was verified to be authentic and complete. Both GLP and non-GLP studies should include independent monitoring and assessments with full disclosure of study findings, including the raw data.

Discussions with FDA on study protocols, including the evaluation of operator technique, safety outcomes, and the effects of the biological system on the device, are encouraged prior to the initiation of *in vivo* animal studies.

5.5. Prior clinical information

For early feasibility studies, although clinical data may not be available for the test device for its proposed intended use, relevant background clinical information should be provided in the Report of Prior Investigations, and may include data or publications on:

- similar or related devices utilized for the proposed intended use; or
- the subject device or similar devices used for a different purpose.

This information, if available, may come from clinical use outside of the United States and may be used to support proof of principle and/or to address the likelihood of potential failure modes that may be observed during the early feasibility study. If such clinical data are available, a clinical study report should be provided.

6. Investigational Plan

The requirements in 21 CFR 812.25 apply to the Investigational Plan for early feasibility study IDE applications. The information in this section is intended to clarify how certain of these requirements apply to early feasibility studies. In an IDE application, the study should be clearly designated as an early feasibility study that is not intended to capture data that would be sufficient to support a marketing application. The proposed study should reflect the novelty of the device and medical need. Use of the pre-IDE process to discuss the Investigational Plan with FDA is highly recommended.

6.1. Risk analysis and mitigation

The Investigational Plan must include a thorough risk analysis which describes the type and potential severity of risks to the subjects, how they will be minimized, and a justification that the risks are reasonable in relation to the expected benefits.⁸ The risk analysis should take the availability of alternative therapies or analyses into consideration.

The Investigational Plan should also include appropriate risk mitigation strategies, such as:

- adequate informed consent, as required by 21 CFR Part 50 Subpart B (see Section 6.3.1);
- use of study sites that have a sufficient level of clinical expertise and support to manage adverse events that may arise and to provide appropriate alternative therapies if needed;
- identification of qualified investigators with adequate training to conduct the early feasibility study;
- a plan to capture human factors information during the course of the study to modify the procedures or device as necessary based on the information obtained;
- specifying relevant study inclusion and exclusion criteria;
- limiting the sample size to a number appropriate for an early feasibility study (e.g., 5-10 subjects);
- appropriate follow-up assessments at regular intervals to monitor subject safety and device effectiveness (i.e., potentially more frequent than for a traditional feasibility or pivotal study);
- timely reporting of serious adverse events (e.g., after each occurrence rather than only in a periodic progress report);
- timely reporting of device performance parameters, which help determine whether the device functions as intended (e.g., measurements of deliverability, stability, handling, visualization, patency, integrity);
- initial device use in subjects with more favorable anatomical characteristics as compared to the population eligible for the early feasibility study (e.g., selecting subjects that meet study eligibility requirements but do not have anatomic features that may increase the difficulty of the device use); and
- description of a pre-specified plan for periodic patient outcome assessments (e.g., as frequently as after each use of the device) and reporting prior to enrollment of additional patients.

6.2. Clinical protocol

The Investigational Plan for early feasibility studies must present objectives that reflect the purposes of the clinical study.⁹ The study protocol should include study endpoints, endpoint assessment methods, and adverse event definitions as appropriate for an early feasibility study.

The study protocol must also clearly describe the methodology to be used in the investigation.¹⁰

This should include a description of the subjects to be included in the study. The subjects may have different clinical characteristics as compared to the population to be included in a future pivotal study (e.g., the early feasibility cohort may have more comorbidities, or a more advanced stage of disease). In addition, the study protocol must include an analysis of the protocol demonstrating that the investigation is scientifically sound.¹¹ Thus, to ensure that the study will provide information useful for the device development process, and to avoid exposing subjects to risks in the absence of any potential benefit, the study should avoid enrolling subjects for whom success is unlikely due to general health issues. The protocol generally does not need to include the same level of detail as a pivotal study protocol, as previously discussed in Section 5; however, it needs to ensure adequate capture of adverse clinical events and device performance information.

6.3. Human subject protection measures

Human subject protection measures including informed consent and ethics committee oversight,¹² should be tailored to the subject population and the risk profile of the device under investigation.

6.3.1. Informed consent

The informed consent process for early feasibility studies, as for all clinical investigations, must adhere to the requirements described in 21 CFR Part 50 Subpart B – Informed Consent of Human Subjects. An informed consent form for early feasibility studies must comply with the requirements in 21 CFR 50.25. For example, subjects must be told that the study involves research and must be provided an explanation of the purposes of the research,¹³ including that the proposed investigation is an early feasibility study (e.g., a small study of an innovative device or innovative clinical use of a device for which there is less nonclinical data than would be required for a larger study). The novelty of the device or procedure should also be described in language understandable to the subject.

As discussed above, due to the reduced amount of information needed to commence an early feasibility study, these studies may carry greater inherent risk, especially unknown risk, as compared to traditional feasibility and pivotal studies. Subjects must be made aware during the informed consent process that there may be unforeseeable risks associated with participation in the study due to limitations in available data and experience with the device.¹⁴ A description of any benefits to the subject or to others which may reasonably be expected from the research must be provided during the informed consent process in accordance with 21 CFR 50.25(a)(3). For example, the form should note that even if there is limited or no personal benefit to the study subject, future patients with the disease or condition may benefit from the information obtained during the early feasibility study. However, the consent form should not include language that could lead subjects to overestimate the chance of personal benefit.

6.3.2. Institutional Review Boards

As with all clinical investigations, early feasibility studies must adhere to the requirements for study oversight by an IRB, as described under 21 CFR Part 56. For example, IRBs must consider whether the risks to the subjects are reasonable in relation to anticipated benefits and the importance of the knowledge that may be expected to result, as well as ensure that risks to the subjects are minimized to the extent possible.¹⁵

IRBs must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year, as required by 21 CFR 56.109(f). It is likely that more frequent oversight by the IRB to assure human subject protection may be appropriate for early feasibility studies. This may include, for example, continuing review on a more frequent basis than annually, continuing review after a small target number of subjects have been studied, and/or graduated enrollment based upon safety analysis of the preceding subjects.

6.4. Monitoring

6.4.1. Monitoring procedures

Detailed monitoring procedures, appropriate for an early feasibility study, must be included in the Investigational Plan under 21 CFR 812.25(e). For information on standard monitoring procedures see FDA's draft guidance, "Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring".^{3,16} The monitoring procedures for early feasibility studies may deviate from the standard monitoring procedures and should be tailored to the particular study being conducted.

6.4.2. Data monitoring committee (DMC)

FDA's guidance, "Establishment and Operation of Clinical Trial Data Monitoring Committees",^{4,17} notes that:

[E]arly studies are often exploratory in nature; they are frequently not randomized or controlled and therefore accumulating results are known to the investigators and sponsor. Issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting. Nevertheless, for difficult situations in which the potential scientific gain from continuing a study must be evaluated in the context of ethical considerations for ensuring subjects' rights and welfare, particularly in settings such as those described above, DMCs may be helpful to investigators, sponsors, and IRBs by providing independent, objective expert counsel.

For certain early feasibility studies, a DMC composed of clinicians, scientific experts, and individuals with ethical expertise may be helpful in evaluating data relatively early on in the course of the study and would provide an additional layer of human subject protection. Use of a DMC could be helpful and may be proposed by a sponsor as an element of its risk mitigation strategy, particularly for studies where additional independent oversight would be of value.

7. Iterations during early feasibility studies

Because modifications to the Investigational Plan are expected during early feasibility studies, discussions with FDA to facilitate timely implementation of changes are particularly important throughout the pre-IDE and IDE processes. The requirements outlined in 21 CFR 812.35 and explained in, “Changes or Modifications During the Conduct of a Clinical Investigation; Final Guidance for Industry and CDRH Staff”,¹⁸ regarding changes to a device or clinical protocol apply to all types of investigational studies. However, this early feasibility guidance adopts a new policy, interpreting the requirements differently for these studies.

To facilitate timely device and/or clinical protocol modifications during an early feasibility study this guidance announces the following approaches:

1. Permitting a broader array of modifications to the device and the clinical protocol under 5-day notification without prior FDA approval during an early feasibility study than during other types of studies;
2. For anticipated changes that would require prior FDA approval, a sponsor may seek **contingent approval** beforehand, which would permit changes contingent upon acceptable nonclinical test results without requiring additional FDA action;
3. For early feasibility study IDE supplements, FDA intends to utilize a new **interactive review** process that encourages communication with FDA during the 30-day review cycle.

Please note that certain changes must be reported in the annual progress report to the IRB required by 21 CFR 812.150(b)(5).¹⁹ In addition, the changes may be subject to IRB review procedures under 21 CFR 56.110.

7.1. Changes requiring FDA notification (5-day notice)

For all IDEs, a sponsor may make certain changes to an investigational device or clinical protocol during the study without prior FDA approval of a supplemental application by submitting a notice to FDA within 5 days of making the change.²⁰ A sponsor may make changes with 5-day notice if: (i) the changes to device development 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 the investigation; or (ii) the changes to the clinical protocol do not affect the (a) validity of the data or information, or the relationship of likely patient risk to benefit relied upon to approve the protocol; (b) the scientific soundness of the plan; or (c) the rights, safety, or welfare of the human subjects involved in the investigation.²¹ The information to be included in such a notice is described in 21 CFR 812.35(a)(3)(iv).

For early feasibility studies 5-day notices may be used in the following manner:

Device developmental changes that do not constitute a significant change in design or basic principles of operation are appropriate for 5-day notices. For early feasibility studies, we would consider a broader range of changes not to be significant than we would for other types of studies. This is in part because the evaluation of early feasibility studies does not depend on statistically significant analyses of data collected or on pooling data among study subjects. However, the changes should be expected not to adversely affect device performance or pose additional risk to the study subjects. The types of changes that may be considered for 5-day

notices may be prospectively identified within the IDE application to facilitate timely implementation of potential improvements.

For changes to an early feasibility study clinical protocol, sponsors should particularly focus on the requirements for 5-day notice that the changes not: (1) alter the relationship of likely subject benefit and risk relied upon to approve the protocol, or (2) affect the rights, safety or welfare of study subjects.²² Since, as discussed above, early feasibility studies are expected to have enhanced risk mitigation strategies and patient protection measures directed toward each study subject, sponsors should explain how these instruments provide additional support when considering changes appropriate for implementation under a 5-day notice. The other criteria, specifically, that changes to the clinical protocol not affect the validity of the data or the scientific soundness of the investigational plan,²³ should generally be much easier to meet for early feasibility studies than for other studies because these studies are not intended to obtain statistically valid data or test statistical hypotheses.

Appendix 2 includes examples of the types of changes that may be appropriate for 5-day notification during an early feasibility study.

7.2. Changes requiring FDA approval²⁴

The first step in obtaining FDA approval of changes during the early feasibility study should be informal discussion with FDA to identify the proposed modifications, the reasons for the modifications (e.g., adverse events observed during the clinical study), the purpose of the modifications, and the evaluations needed to support use of a modified device and/or changes to the clinical protocol.

Following the informal discussion, there are two new approaches for obtaining timely FDA approval of changes. This guidance adopts the following new approaches for obtaining timely FDA approval of changes to early feasibility studies: 1) contingent approval and 2) interactive review.

1) Contingent approval. When device iterations or changes to the clinical protocols are anticipated, identified, and explained prospectively, the contingent approval process may be used. This process may be proposed during the original early feasibility study IDE application or in IDE supplements.

In order to obtain contingent approval, during the 30 day review cycle the sponsor and FDA should reach final concurrence on and document the nonclinical test plan and associated acceptance criteria to evaluate the anticipated changes. Once these are agreed upon, FDA may approve the anticipated changes contingent on the sponsor's successful completion of the test plan, and the reporting of the test data to FDA within 10 calendar days of implementing the change.

If the sponsor deviates from the conditions of FDA's approval, the contingent approval would no longer be valid, and the sponsor would need to renegotiate the test plan with FDA and obtain a new contingent approval. Alternatively the sponsor could seek approval through the submission of a 30-day IDE supplement.

If the sponsor is able to anticipate multiple potential device iterations and can prospectively identify the appropriate testing plan and acceptance criteria for each type of change, a proposal that covers all the changes may be provided in the original early feasibility IDE application or in a single supplement. For example, if a sponsor anticipates iterations of the materials of construction based on clinical data generated during the early feasibility study, they may present their strategy in a single IDE supplement and receive approval for the iterative plan contingent on successful completion of the test plan for each material type. For modifications to the clinical protocol, this could include pre-defining several clinical parameters and acceptable values for each that may be added or removed during the study to allow investigators to determine the most relevant parameters for future evaluation of the device. Within 10 days of implementing each change, an IDE supplement should be submitted to provide the data and to report to FDA the current device iteration being used in the study.

Appendix 2 includes examples of the types of changes that may be appropriate for contingent approval during an early feasibility study.

2) **Interactive review.** Interactive review involves the continuation of informal discussions with FDA during the 30-day IDE supplement review cycle. This process may be used in situations where the sponsor has completed nonclinical testing to evaluate device modifications, or where changes to the clinical protocol do not meet the criteria for a 5-day notice, and FDA decides that the additional information needed to address outstanding questions can be provided and reviewed within the 30-day review cycle. The sponsor should submit an official request for the modifications that incorporates the information previously communicated to FDA and prior FDA feedback. During interactive review, FDA may request, and the sponsor may provide, additional information to enable the approval of the supplement within 30 days. The success of the interactive review process depends on the availability of FDA and sponsor resources to provide timely and high quality feedback, as well as the acceptability of the test results.

8. Next steps in clinical evaluation

After obtaining clinical information from an early feasibility study, the type of subsequent clinical evaluation will depend on the stability of the device design, the availability of adequate data to justify the next study, and the purpose of that clinical study. Early feasibility studies involve the investigation of devices that may be in a rapid phase of device iteration. If clinical information is needed after device modification and further device iterations are expected, sponsors may submit an IDE supplement including a request for expansion of the early feasibility study to FDA. Once approved, the sponsor may enroll additional subjects in the early feasibility study. If the device design is near-final or final, and the results of the early feasibility study support the initial safety of the device and proof of principle, it may be more appropriate for the sponsor to pursue either a traditional feasibility study or a pivotal study. At this point, further informal communications with FDA are important to help determine the most appropriate study, which will ultimately depend on the amount of nonclinical and clinical data available to the sponsor to justify the study. Progression to a traditional feasibility or pivotal study should be requested under an IDE supplement and should include the information needed to justify initiation of the larger study.

9. Conclusion

Early feasibility studies provide early device safety data and clinical verification of the proof of principle. Data from an early feasibility study may lead to device modifications and be used to refine the bench, analytical, and *in vivo* animal studies and future clinical study protocols.

Conducting an early feasibility study under an IDE provides a unique opportunity to obtain clinical experience with a new or modified device or new clinical use, while utilizing appropriate subject protection measures and good clinical study practices. Vital clinical information can be captured and used to optimize the device design, design evaluation, and clinical investigation plans.

Initiation of an early feasibility study and progression towards a pivotal study benefit from a flexible process that relies on sound nonclinical assessments and appropriate risk-based rationales. A high degree of interaction between FDA and the sponsor and use of the pre-IDE process will be instrumental in the successful implementation of this guidance.

Appendix 1: Device Evaluation Strategy Example

The following hypothetical example of an acceptable proposal further illustrates the concepts described in Section 6.2.2.

A sponsor approaches FDA with a proposal to evaluate an innovative, metallic implant to treat a disease common in the elderly in an early feasibility study. The device is unique in that delivery of the treatment will be through a novel catheter design, rather than through the standard procedure that involves open surgery. There are some aspects of the new device that are similar to an approved device.

The sponsor has described the design concept in detail to support the sponsor’s device evaluation strategy. In order to obtain FDA feedback regarding the sponsor’s longer-term evaluation plans, the sponsor has included proposals for the information/data needed to support progression to each of their planned developmental phases in addition to that needed to support initiation of the early feasibility study under a pre-IDE submission.

A portion of the device evaluation strategy provided by the sponsor is included in Table 1.

Table: Device Evaluation Strategy Example

Device/ Procedure Related Function	Potenti al Failure Modes	Potential Effects of Failure		Information/Data			
		Device	Clinical	Early Feasibility/FIH	Traditional Feasibility*	Pivotal	Marketing
Implant integrity	Structur al failure of implant	Metallic fracture	Exacerbation of treated problem Foreign body embolization	Discussion on design concept to optimize integrity	Early feasibility clinical data If device modified:	Limited number of cycles for durability testing	Full number of cycles of durability testing

			Trauma to adjacent structures	Comparison of design to marketed devices Strength testing Stress/ strain analysis	Strength testing on modified device, if appropriate Stress/ strain analysis on modified device, if appropriate	Bench testing and fatigue analysis on final device design Clinical data	Clinical data
	Corrosion	Metallic fracture	Exacerbation of treated problem Foreign body embolization Trauma to adjacent structures	Comparison of materials to marketed devices	Corrosion testing	If device modified: Assessment of modifications on corrosion potential, with new testing if necessary	Clinical data
Appropriate biological response	Loss of device function	None	Necrosis	Comparison of design and materials to marketed devices Acute and medium-term implantation in an appropriate animal model	Early feasibility clinical data If device modified: Repeat acute and medium- term animal study, if appropriate	Longer-term implantation in a validated animal model Feasibility clinical data	Clinical data

* It may not be necessary to conduct a traditional feasibility study following an early feasibility study.

As shown in the Early Feasibility Information/Data column, the sponsor proposes to address the need for device structural integrity for their early feasibility study through discussion of the design concept and other relevant experience, supplemented by basic strength testing and a stress/strain analysis. The new device design has similarities to a device that is in clinical use; thus, some information can be leveraged to support the assessment of the structural integrity of the new device. The sponsor indicates that a loss of device integrity would not lead to a catastrophic failure and that subjects would be closely monitored to allow detection of any loss of device integrity.

The sponsor proposes that similar testing and analyses would be needed to support a traditional feasibility study, with the addition of corrosion testing and clinical data from the early feasibility study. Progression to a pivotal study would include submission of limited durability testing results, which will be supplemented by fatigue analysis (i.e., a finite element analysis) of, and additional bench testing on, the final device design. Complete durability testing would be needed to support a marketing application. The clinical data would further support the implant integrity in the marketing application.

An animal study in a validated animal model to evaluate the potential for catastrophic failure of the device acutely and in the medium term is proposed to justify the initiation of an early feasibility study. A longer-term animal study would be completed to demonstrate complete healing at later time points.

Appropriate changes in the device evaluation strategy will be made as information is obtained from the early feasibility study.

Appendix 2: Device iteration example

The following is a hypothetical scenario that illustrates the concepts described in Section 7 regarding device iteration during an early feasibility study.

A sponsor approaches FDA with a proposal to evaluate an innovative device in an early feasibility study to treat a disease common in the elderly. The device is unique in that delivery of the treatment will be through a novel catheter design, rather than through the standard procedure which involves open surgery. The sponsor proposes to enroll up to 10 subjects at up to 3 investigational sites. The sponsor will evaluate the device performance and clinical outcomes after each subject is treated, and prior to enrolling the next subject. Based on these assessments, they will consider device and clinical protocol modifications.

In their original IDE application the sponsor seeks contingent approval for several types of changes. They propose the following specific iterative changes that they would like FDA approval for implementing as they complete their pre-specified device evaluation plan:

- improvements in maneuverability, including:
 - modifying the shape of the nose cone of the introducer (e.g., make sharper or more blunt); and
 - making the sheath stiffer or more flexible;
- changing the length of the catheter to allow for the use of alternative access sites;
- modifying the hemostatic valve by changing material properties or device dimensions to improve hemostasis or reduce friction;
- implementing ergonomic changes in the handle that do not affect the overall function of the device (e.g., changing texture of knobs or handle);
- adding, moving, or changing the radiopaque bands on the catheter to improve visibility; and
- modifying the operator interface console.

The sponsor and FDA reach concurrence on the test plan to evaluate the proposed changes through informal discussions that are subsequently documented in the original IDE submission. Although some of these changes may have been appropriate for 5-day notices, obtaining prospective, contingent approval provides the sponsor with more predictability in the regulatory process for their device modification plans.

With help from their principal investigator, the sponsor identified other types of changes that may be needed for their device and clinical protocol during the conduct of their early feasibility study and discussed these with FDA under a pre-IDE. The sponsor includes the following table in their original IDE to describe their plan.

[Click Here to Go to the Table of Contents](#)

Table: Regulatory Process for anticipated modifications

Changes that may be appropriate for 5-day notification	Changes that may be appropriate for contingent approval	Changes that may be appropriate for 30-day interactive IDE supplement
Addition of surface coating to catheter if lubricity is needed to improve access*	If a surface coating is added, need to modify the distribution, thickness or area covered by the coating	Expand the subject selection criteria (e.g., inclusion of younger subjects than defined in the original protocol)
Change specific features of the device to be consistent with device approved for use under another IDE for a similar indication*	Modification to improve catheter resistance to kinking, with the type of modification and appropriate testing to be identified prior to supplement submission	Changes identified as necessary during the early feasibility study for which the testing needed would be different from that previously used or where it is difficult to determine reasonable acceptance criteria for the testing
Changes in the device preparation for use	Changing the device to accommodate a broader range of subject anatomies (i.e., type of modification and therefore type of appropriate testing not identified in the original IDE)	Change from percutaneous access to an open cutdown or to use of a vascular conduit
Addition of use of approved ancillary device intended to improve the safety of the procedure*	Other device modifications identified during the clinical study for which an appropriate testing plan and acceptance criteria can be identified	
Use of off the shelf tools (i.e., that were not identified in the original IDE) to perform bailout procedures		
Modification to subject selection to limit, rather than expand, the criteria*		
Modify procedural imaging modalities*		
Reducing follow-up assessments if early data support change (i.e., show that the change would not affect the safety of the subjects)*		
Change case report forms to capture additional information		

* These types of changes would not generally be appropriate for 5-day notification in a pivotal study due to their possible effect on the scientific soundness of the investigational plan and/or data validity.

Many of the types of changes that might be appropriate for 5-day notification during this early feasibility study would not normally be acceptable for studies enrolling a larger number of subjects or in a study intended to collect data to independently support a marketing application. However, for this early feasibility study, the changes proposed to the device and clinical protocol would not adversely alter the risks for the study subjects. The developmental device changes would be appropriate for 5-day notification because they:

- are reasonably defined such that appropriate testing and expected outcomes are known;
- do not constitute significant changes in the basic principles of operation; and
- are not considered significant because they would not adversely affect the interpretability of the results of an early feasibility study, and would not be expected to adversely affect device performance or to be associated with additional risk to the study subjects.

Similarly, the clinical protocol changes would be appropriate for 5-day notification because the changes do not affect:

- subject safety, rights, or welfare, because enhanced subject protection measures are in place for the early feasibility study;
- the validity of the data or information resulting from the completion of the approved protocol because the such data or information will not be pooled;
- the relationship of likely patient risk to benefit relied upon to approve the protocol; or
- the scientific soundness of the study because there are no statistical hypotheses to be tested in the early feasibility study.

During the course of the sponsor's early feasibility study, the sponsor made some of the anticipated changes, but also identified an additional modification that had not been predicted in the original IDE submission which the sponsor described to FDA informally. The sponsor requested contingent approval of a change in a material used in the construction of the device based on obtaining acceptable results for this material using same types of testing used to evaluate the original device design. To formally request this change, the sponsor submitted an IDE supplement that described the change and evaluation plan. FDA and the sponsor reached a consensus regarding the proposal during the 30-day review time for the supplement, and FDA granted approval of the modification contingent on the sponsor's successful completion of the proposal and reporting of the change and supporting information to FDA within 10 days of implementing the change. The sponsor evaluated the modified device according to the test plan, obtained acceptable results, implemented the change and submitted their test report to FDA 7 days after making the change.

¹ *Significant risk device* is defined at 21 CFR 812.3(m) 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;
- (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.

² Additional testing could be completed concurrent with conducting the early feasibility study if needed to support the conduct of a traditional feasibility or pivotal study.

³ Note that this guidance does not recommend that sponsors prematurely initiate clinical testing when further useful and appropriate nonclinical testing can be performed for the particular device the sponsor is developing.

⁴ 21 CFR 812.20(a).

⁵ 21 CFR 812.27(a).

⁶ Characterization tests (i.e., testing conducted to describe the device) may not have specified acceptance criteria.

⁷ At the early feasibility stage, a descriptive risk analysis may be more informative than a formal failure modes and effect analysis (FMEA), which provides a quantitative ranking of risks.

⁸ See 21 CFR 812.25 and 812.30(b)(4).

⁹ 21 CFR 812.25(a).

¹⁰ 21 CFR 812.25(b).

¹¹ 21 CFR 812.25(b).

¹² See 21 CFR Parts 50 and 56.

¹³ 21 CFR 50.25(a)(1). For more information on Informed Consent see, "[A Guide to Informed Consent - Information Sheet](#)"⁶."

¹⁴ See 21 CFR 50.25(b)(1).

¹⁵ 21 CFR 56.111(a)(1) and (2).

¹⁶

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>⁷

¹⁷ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>⁸

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082145.htm>⁹

¹⁹ See 21 CFR 812.35(a)(4).

²⁰ 21 CFR 812.35(a)(3).

²¹ 21 CFR 812.35(a)(3)(i) and (ii). These changes must be supported by credible information as defined at 21 CFR 812.35(a)(3)(iii).

²² See 21 CFR 812.35(a)(3)(ii).

²³ 812.35(a)(3)(ii)(A) and (B).

²⁴ See 21 CFR 812.35(a)(1).

**Appendix 9: FDA Guidance for Clinical Investigators, Sponsors, and IRBs:
Investigational New Drug Applications (INDs) – Determining Whether
Human Research Studies Can Be Conducted Without an IND**

NOTE: A stay is in effect for parts of subsection VI.D of this guidance. Additional information about this stay can be found in the Notice of Stay that published in the *Federal Register* of October 30, 2015 (80 FR 66907).

**Guidance for Clinical
Investigators, Sponsors, and
IRBs**

**Investigational New Drug
Applications (INDs) –
Determining Whether Human
Research Studies Can Be
Conducted Without an IND**

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

September 2013
Clinical/Medical

**Guidance for Clinical Investigators,
Sponsors, and IRBs**

**Investigational New Drug Applications
(INDs) — Determining Whether Human
Research Studies Can Be Conducted
Without an IND**

Additional copies are available from:

*Office of Communications,
Division of Drug Information, WO 51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Rockville, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov*

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

and/or

*Office of Communication, Outreach and
Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Phone: 800-835-4709 or 301-827-1800*

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

and/or
Outreach and Information Center
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740
Phone: 888-723-3366

<http://www.fda.gov/Food/GuidanceRegulation/default.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)
Center for Food Safety and Applied Nutrition (CFSAN)

September 2013
Clinical/Medical

TABLE OF CONTENTS

I. INTRODUCTION	1
II. BACKGROUND	2
III. RESEARCH STUDIES THAT REQUIRE AN IND	2
What Is a Drug?	3
What Is a Clinical Investigation?	4
IV. CLINICAL INVESTIGATIONS THAT ARE EXEMPT FROM THE IND REQUIREMENTS BY REGULATION	4
Certain Research Involving Marketed Drug Products	4
Bioavailability or Bioequivalence Studies in Humans	8
V. HUMAN RESEARCH STUDIES INVOLVING RADIOACTIVE OR COLD ISOTOPES.....	8
Radioactive Isotopes	8
Cold Isotopes	9
VI. SPECIFIC ISSUES CONCERNING THE APPLICATION OF THE IND REGULATIONS	9
A. Endogenous Compounds	10
B. Live Organisms	10
Cosmetics	10
Foods [†]	11
Research With Noncommercial Intent	15
VII. FREQUENTLY ASKED QUESTIONS	15
VIII. PROCESS FOR ADDRESSING INQUIRIES CONCERNING THE APPLICATION OF THE IND REQUIREMENTS	18
APPENDIX	20

† Part of this subsection is stayed.

i

Guidance for Clinical Investigators, Sponsors, and IRBs^x

Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND

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

I. INTRODUCTION

This guidance is intended to assist clinical investigators, sponsors, sponsor-investigators,^{xi} and institutional review boards (IRBs) in determining whether research studies involving human subjects must be conducted under an investigational new drug application (IND), as described in title 21 of the Code of Federal Regulations, part 312 (21 CFR part 312) (the IND regulations). This guidance describes when an IND is required, specific situations in which an IND is not required, and a range of issues that, in FDA's experience, have been the source of confusion or misperceptions about the application of the IND regulations.^{xii} This guidance addresses only whether an IND is needed. If your

^x This guidance has been prepared by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration (FDA or the Agency).

^{xi} The definitions in the IND regulations describe specific roles for the individual or individuals who conduct a clinical investigation (the investigators) and the individual or entity who has primary responsibility for and initiates the clinical investigation (the sponsor) (§ 312.3(b)). In the most common scenario, a commercial sponsor has primary responsibility for and initiates the clinical investigation, and multiple investigators are responsible for the actual conduct of the investigation at their respective study sites. The term *sponsor-investigator* typically refers to an individual at an academic institution who takes responsibility for, initiates, and conducts a clinical investigation at a single site (sometimes referred to as an *investigator-initiated study*) and therefore meets the definition of both a sponsor and an investigator for purposes of the IND regulations.

^{xii} This guidance does not address expanded access to investigational drugs for treatment use under subpart I of 21 CFR part 312.

study also involves the use of a device, you should determine whether such use is subject to 21 CFR part 812 (the IDE regulations).

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

II. BACKGROUND

FDA has two primary objectives in reviewing an IND: (1) to assure the safety and rights of subjects in all phases of an investigation and (2) in phases 2 and 3, to help assure that the quality of the scientific evaluation of the drug is adequate to permit an evaluation of the drug's effectiveness and safety (21 CFR 312.22).

FDA receives frequent inquiries from the academic community (e.g., clinical investigators, IRBs) and the pharmaceutical industry about whether an IND should be submitted for various types of clinical research. Inquiries have related to a range of issues concerning application of the IND requirements in part 312, including, for example:

- Clinical investigations using marketed drugs
- Bioequivalence/bioavailability studies
- Studies using radiolabeled or cold isotopes
- Studies using dietary supplements or foods
- Studies using endogenous compounds
- Pathogenesis studies using modified organisms
- Studies using wild-type organisms in challenge models
- Studies that do not have a commercial purpose

Because of the large number of inquiries and wide range of issues, FDA determined that it would be helpful to provide to potential sponsors, clinical investigators, and sponsor-investigators an overview of the IND requirements and related issues.

With certain exceptions, clinical investigations in which a drug is administered to human subjects must be conducted under an IND as required in part 312. Sections III, IV, and V of this guidance elaborate on the criteria for when a study must be conducted under an IND; the types of studies that involve drugs, but that are exempt from the IND requirements; studies involving radioactive drugs that are generally recognized as safe and effective (and to

which IND requirements therefore do not apply); and FDA’s use of enforcement discretion with respect to certain studies using cold isotopes conducted without an IND. Section VI discusses specific issues that frequently arise concerning application of the IND regulations; section VII contains frequently asked questions; and section VIII describes the process for seeking advice from FDA concerning the application of the IND regulations to a planned clinical investigation.

III. RESEARCH STUDIES THAT REQUIRE AN IND

In general, the IND regulations in part 312 require that human research studies be conducted under an IND if all of the following conditions exist:

- The research involves a *drug* as that term is defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 321(g)(1)).
- The research is a *clinical investigation* as defined in the IND regulations (21 CFR 312.3).
- The clinical investigation is not otherwise *exempt* from the IND requirements in part 312 (see section IV of this guidance).

A. What Is a Drug?

The definition of the term *drug* in section 201(g)(1) of the FD&C Act includes, among other things, “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . .” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” Biological products subject to licensure under section 351 of the Public Health Service Act (42 U.S.C. 262) may also be considered drugs within the meaning of the FD&C Act. A *biological product* is:

. . . a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), 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.

(42 U.S.C. 262(i))

Biological products include, among other products, bacterial vaccines, allergenic extracts, gene therapy products, growth factors, cytokines, and monoclonal antibodies.

[Click Here to Go to the Table of Contents](#)

It is important to note that the *drug* definition is not limited to compounds intended for a therapeutic purpose.^{xiii} The definition also includes compounds intended to affect the structure or function of the body, without regard to whether the compound is intended to influence a disease process. For example, the definition includes compounds administered to healthy individuals to prevent pregnancy or treat male pattern baldness. The definition also includes compounds used for research purposes in healthy subjects to blunt or provoke a physiologic response or study the mechanism of action or metabolism of a drug (see section VI.A). Note, however, that (1) a dietary supplement intended only to affect the structure or function of the body and not intended for a therapeutic purpose is not a drug^{xiv} (see section VI.D.1) and (2) a food used as such (i.e., primarily for its taste, aroma, or nutritive value) and not for a therapeutic purpose or to affect the structure or function of the body, other than by providing nutrition, is not a drug (see section VI.D.2).^{xv}

B. What Is a Clinical Investigation?

The IND regulations in § 312.3(b) define *clinical investigation*^{xvi} as:

. . . [an] experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of [the IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a marketed drug in the course of medical practice.

For example, a randomized trial evaluating an unapproved use of a lawfully marketed drug is a clinical investigation and may require an IND.^{xvii} In contrast, use of a lawfully marketed drug for an unapproved use in the course of medical practice is not a clinical investigation and does not require an IND because it involves the use in an individual patient where the primary intent is to treat the patient.

IV. CLINICAL INVESTIGATIONS THAT ARE EXEMPT FROM THE IND REQUIREMENTS BY REGULATION

^{xiii} In this guidance, the term *therapeutic purpose* is intended to encompass diagnosis, cure, mitigation, treatment, and prevention of disease.

^{xiv} See 21 CFR 101.93(f) and (g); 65 FR 1000 (Jan. 6, 2000).

^{xv} See 21 U.S.C. 321(f) and (g)(1); *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir. 1983)).

^{xvi} Additional information on clinical investigations is available on FDA's Web site at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>.

^{xvii} See section IV.A of this guidance.

FDA regulations describe two categories of clinical investigations that are exempt from the IND requirements in part 312, provided the criteria for exemption are met (see 21 CFR 312.2(b) and 320.31(b)). The two categories of clinical investigations and the applicable criteria are described in the following subsections. Ordinarily, clinical investigations of drugs that do not meet these criteria must be conducted under an IND as required in part 312.

A. Certain Research Involving Marketed Drug Products

Whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation. A clinical investigation of a *marketed* drug is exempt from the IND requirements if *all* of the criteria for an exemption in § 312.2(b) are met:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

The potential sponsor or sponsor-investigator of a planned clinical investigation using a marketed drug is responsible for determining whether the investigation meets the criteria for an exemption.^{xviii} If there is uncertainty about whether the exemption criteria are met, the potential sponsor or sponsor-investigator

^{xviii} The preamble to the rule finalizing the IND regulations provides:

FDA recognizes that a considerable amount of professional judgment must be exercised in determining whether the conditions of an investigation “significantly increase” the risk associated with use of the drug. Because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption. (See the final rule on New Drug, Antibiotic, and Biologic Drug Product Regulations that published in the *Federal Register* of March 19, 1987 (52 FR 8798 at 8802)).

can seek advice from FDA on the applicability of the IND regulations (§ 312.2(e)).

Three of the criteria for exemption listed previously merit further discussion.

- What is meant by a *drug product that is lawfully marketed in the United States*?

The preamble to the final rule incorporating the IND exemption criteria into the IND regulations makes clear that the exemption provision was not intended to require use of only the marketed version of the drug product for a clinical investigation to be exempt from the IND requirements. The intent was to provide some latitude to modify the marketed version of the drug product for use in a clinical investigation. In responding to comments asking FDA to clarify to what extent a sponsor could change the marketed drug product or conditions of use and still be exempt from the IND regulations, FDA stated that:

The exemption was not intended to require an investigator to use the drug in exactly the same dosage form, dosage levels, and patient populations described in the marketed labeling for the product, but rather to permit changes to the lawfully marketed drug product that do not increase the risks . . . over the risk presented by use of the product in conformance with its marketed labeling.^{xix}

Therefore, sponsors or sponsor-investigators can make low-risk modifications to the lawfully marketed dosage form to, for example, blind a study.

In making modifications to the marketed dosage form, sponsors and sponsor-investigators should consider the potential risk implications of the modifications based on the type and complexity of the dosage form. For example, minor variations to solid oral dosage forms, such as changing the color, scoring, or capsule size of the marketed dosage form for blinding purposes, would generally be low risk, provided the changes did not involve major manufacturing or formulation changes. Similarly, using capsules to over-encapsulate the marketed dosage form would generally be low risk, provided the capsule met appropriate standards. Changes to more complex oral dosage forms and injectable and other non-oral dosage forms might carry greater risk. Products that are very sensitive to conditions in their environment (e.g., protein products) also carry greater risk because changes to the formulation, dosage form, manufacturing, or primary packaging

^{xix} Final rule, “New Drug, Antibiotic, and Biologic Drug Product Regulations” (52 FR 8798 at 8801, March 19, 1987).

might change the pharmacokinetics, immunogenicity, or other characteristics of such products.

Given the range of possible modifications to a marketed dosage form, FDA cannot provide comprehensive guidance on the degree of risk presented by all such modifications. If sponsors or sponsor-investigators have concerns about whether changes to a lawfully marketed dosage form increase risk to an extent that an IND would be required, they should consult FDA (see section VIII). If a sponsor or sponsor-investigator consults FDA, they should provide FDA with a listing of chemistry, manufacturing, and controls (CMC) variations from the marketed version of the drug product, if CMC information for the marketed product is available to them, and any other pertinent information that would assist FDA in responding to an inquiry.

- Is the risk associated with the product significantly increased (or the acceptability of the risk significantly decreased)?

Historically, assessing whether a particular use of a drug in a clinical investigation significantly increases the risk or decreases the acceptability of the risk, compared to its approved use or uses, has been the most difficult issue in determining whether an IND is needed for a clinical investigation of a marketed drug (21 CFR 312.2(b)(1)(iii)). This provision has been particularly difficult in the oncology setting where many of the therapies have significant toxicity; for that reason, FDA has issued guidance to help clinical investigators studying cancer treatments determine whether the risk associated with the use of the drug in a planned clinical investigation is significantly increased or the acceptability of the risk is significantly decreased.^{xx} FDA's cancer treatment guidance is also a useful reference for clinical studies of marketed drugs in other therapeutic areas, particularly for studies in other serious and life-threatening conditions, as the risk-benefit scenarios are at least somewhat relevant to non-oncologic settings. Investigators should carefully consider the risk implications of any conditions of use in the study that deviate from the conditions of use described in the drug's labeling, with particular attention to the following:

- Route of Administration: A change in the route of administration can introduce a significant new risk. For example, there could be a significant increase in risk if a marketed drug for oral administration is converted to a dosage form that is to be administered by injection

^{xx} See the guidance for industry *IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer* (the cancer treatment guidance). We update guidances periodically. To make sure you have the most recent version of a guidance, check the Drugs guidance page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> and the Biologics guidance page at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

- or intravenous, intrathecal, or inhalation route. These other routes of administration introduce concerns with increased local concentrations, sterility, pyrogenicity, hypersensitivity (e.g., airway reactivity), variations in metabolism, and other issues not present with oral administration that can significantly increase the risk, or decrease the acceptability of the risk, associated with use of the drug.
- Dose: Increases in dose, frequency, or duration of administration, compared to labeled dosing regimens, can significantly increase the risk in a study using a marketed drug. It is also possible that a decrease in dose could significantly increase risk. For example, administering a sub-therapeutic dose of an antiviral drug to study subjects could induce resistance in the subjects, thus rendering a subsequent therapeutic dose of the drug ineffective in treating the virus. The significance of changes in dose (in particular, increases in dose) can vary across therapeutic areas. For example, the cancer treatment guidance provides some latitude for conducting studies of high-dose cancer treatments without an IND because oncologists are generally familiar with the implications of high-dose regimens. In other clinical settings, use of higher doses than are recommended in labeling may be much more likely to significantly increase the risk or decrease the acceptability of the risk.
 - Patient Population: The acceptability of known and unknown risks can vary across different treatment populations (see § 312.2(b)(1)(iii)). The population chosen for study could be at increased risk compared to the approved use population for a variety of reasons, such as increased age, different disease or stage of disease, concomitant illness, decreased renal or hepatic function, or concomitant therapy. For example, a drug with significant toxicity can be approved for use in a population with a lifethreatening or severely debilitating disease because the risk of toxicity is acceptable in that population. Use of that drug in a clinical investigation in a population that is not so ill (e.g., to evaluate the drug for prevention of disease or symptomatic relief), however, would present a different risk-benefit situation in which the known risks might not be acceptable. When use of the drug in a specific patient population decreases the acceptability of the known risks, the study would have to be conducted under an IND as required under 21 CFR part 312.
- Does the sponsor intend to (1) report to FDA the investigation as a well-controlled study in support of a new indication, (2) use it to support any other significant change in the labeling of the drug, or (3) use it to

support a significant change in the advertising (for prescription drugs only) for the drug?

Generally, it seems reasonable to infer that any well-controlled trial of a marketed drug (e.g., a study of a new indication) sponsored by the manufacturer of the drug would be intended to be used to influence labeling or promotion in some significant way and would have to be conducted under an IND. On the other hand, similar studies of marketed drugs conducted by an entity that does not have an independent ability to change a drug's labeling – e.g., a study conducted by a sponsor-investigator in an academic setting or Government agency sponsor – would not generally be intended to be submitted to FDA to support a new indication or to otherwise influence the drug's labeling or promotion. However, data from such studies may subsequently be submitted to FDA for that purpose and, therefore, FDA has an interest in helping to ensure that these studies are designed to yield data adequate to support a labeling change. A sponsor who would like to obtain FDA advice on study design can submit an IND for FDA review.

B. Bioavailability or Bioequivalence Studies in Humans

FDA regulations describe criteria under which bioavailability or bioequivalence (BA/BE) studies using unapproved versions of approved drug products can be conducted without submission of an IND (21 CFR 320.31(b) and (d)). Although these regulations are intended to facilitate development of generic drugs, a planned BA/BE study need not be intended for that purpose to be exempt from the IND regulations. A BA/BE study in humans does not require an IND if all of the following conditions are met:

- The drug product does not contain a new chemical entity (21 CFR 314.108), is not radioactively labeled, and is not cytotoxic.
- The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The sponsor meets the requirements for retention of test article samples (21 CFR 320.31(d)(1)) and safety reporting (21 CFR 320.31(d)(3)).

V. HUMAN RESEARCH STUDIES INVOLVING RADIOACTIVE OR COLD ISOTOPES

A. Radioactive Isotopes

FDA regulations (21 CFR 361.1) describe conditions under which radioactive drugs (drugs containing unstable isotopes) can be used for certain research without an IND because they are generally recognized as safe and effective for those uses. These regulations apply to radioactive versions of both approved and unapproved drugs.^{xxi}

Under 21 CFR part 361, human research using a radioactive drug or biological product may be conducted without an IND if (1) it involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product, (2) the use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA, (3) the dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and (4) the total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

B. Cold Isotopes

Cold isotopes (isotopes that lack radioactivity) have been increasingly used for the same research purposes as radioactive isotopes—to obtain basic information about drug metabolism or about human physiology, pathophysiology, or biochemistry. When used for these basic research purposes, cold (or stable) isotopes ordinarily present fewer safety concerns than radioactive isotopes. Unlike radioactive isotopes, however, there is no specific regulation analogous to 21 CFR 361.1 that addresses cold isotopes of approved drugs and unapproved drugs when used for these basic research purposes. However, FDA believes there is no need to have more stringent requirements for studies that use cold isotopes than for those that use radioactive isotopes, and historically, FDA has not objected to studies using cold isotopes being conducted without an IND. In exercising its enforcement discretion, FDA does not intend to object to clinical investigations using cold isotopes of unapproved drugs being conducted without an IND, provided the following conditions are met (the conditions are based on the criteria for studies using radiolabeled drugs (see 21 CFR 361.1)):^{xxii}

^{xxi} For information on determining whether human research with a radioactive drug can be conducted under a Radioactive Drug Research Committee (RDRC), see FDA's guidance for industry and researchers *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application* (the RDRC guidance).

^{xxii} Note that studies using cold isotopes of approved drugs frequently meet the criteria for exemption from the IND requirements in part 312 for studies of marketed drugs (see section IV.A) because the studies involve low doses and present low risk. In such cases, enforcement discretion would not be needed for these studies to be conducted without an IND.

- The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry.
- The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.
- The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.
- The quality of the cold isotope meets relevant quality standards.
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and the requirements for informed consent (21 CFR part 50).

VI. SPECIFIC ISSUES CONCERNING THE APPLICATION OF THE IND REGULATIONS

This section addresses specific issues that frequently arise in discussions with outside parties concerning the application of the IND requirements in 21 CFR part 312.

A. Endogenous Compounds

FDA has received numerous questions concerning the application of the IND requirements to studies in which endogenous compounds are administered to human subjects. A common question is whether *provocation* or *challenge* studies in which an endogenous compound (e.g., bradykinin, histamine, angiotensin) is administered to subjects to evoke a physiologic response, characterize a disease, or establish the mechanism of action are subject to IND requirements. In these cases, the endogenous compound is plainly not being used for a therapeutic purpose. There is, however, intent to affect the structure or function of the body, so the compound would be considered a drug under these circumstances. Therefore, these types of studies are clinical investigations and require an IND under part 312, unless the study meets the criteria for an exemption in § 312.2(b) or § 320.31(b) (see section IV) or the criteria in § 361.1, or the compound is labeled with a cold isotope and used in the manner described in section V, is a dietary supplement (see section VI.D.1), or is an article used for food or drink (i.e., primarily for taste, aroma, or nutritive value, rather than for some other effect on the structure or function of the body) in the study (see section VI.D.2).

B. Live Organisms

An IND is required for challenge studies in which a live organism (e.g., virus, bacteria, or fungi, whether modified or wild-type) is administered to subjects to study the pathogenesis of disease or the host response to the organism (see part 312). Although the challenge organism is not intended to have a therapeutic purpose, there is intent to affect the structure or function of the body. Thus, the organism is both a biological product (see 21 CFR 600.3(h)(1)) and a drug, and an IND is required for the clinical investigation, unless the criteria for exemption in 21 CFR 312.2 are met or the product meets the definition of a dietary supplement^{xxiii} or is an article used for food or drink (i.e., primarily for taste, aroma, or nutritive value, rather than for some other effect on the structure or function of the body) in the study. Similarly, an IND is required for a clinical investigation designed to evaluate whether colonization with a strain of bacteria can treat or prevent disease in patients with a chronic immune disorder.

C. Cosmetics

Section 201(i) of the FD&C Act (21 U.S.C. 321(i)) defines a cosmetic as “(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.” With the exception of color additives and a few prohibited ingredients, a cosmetic manufacturer may use almost any raw material as a cosmetic ingredient and market the product without an approval from FDA.

As a general matter, studies of ingredients or products marketed as cosmetics require an IND if the ingredient is being studied for use to affect the structure or function of the body or to prevent, treat, mitigate, cure, or diagnose a disease (see 21 U.S.C. 321(g)(1); 21 CFR 312.2). This is true even if the study is intended to support a cosmetic claim about the ingredient or product’s ability to cleanse, beautify, promote attractiveness, or alter the appearance, rather than a structure/function claim. For example, a study of the effect of a cosmetic product containing human or animal biological material (such as

^{xxiii} Section 201(ff) of the FD&C Act does not specifically mention live organisms in the definition of a *dietary supplement* (21 U.S.C. 321(ff)), but does include more general language that results in some products containing live organisms falling within the dietary supplement definition, depending on the specific facts related to the product. The relevant language is found in section 201(ff)(1), which lists the substances that may be used as “dietary ingredients” in dietary supplements. Section 201(ff)(1)(E) provides that “dietary substance[s] for use by man to supplement the diet by increasing the total dietary intake” are dietary ingredients; section 201(ff)(1)(F) further defines *dietary ingredient* to include “a concentrate, metabolite, constituent, extract, or combination” of any other dietary ingredient. Taken together, these two provisions indicate that a live organism that is a constituent of an article that is commonly used as human food or drink (e.g., a probiotic in yogurt) may be used as a dietary ingredient in a dietary supplement.

placenta) on skin repair mechanisms would require an IND, even if the study is intended only to support a claim of younger looking skin.

D. Foods

Those who are evaluating published clinical literature or sponsoring new clinical studies while conducting safety assessments for dietary ingredients, food additives (including food contact substances), and GRAS substances, as well as those who conduct or sponsor research intended to support labeling claims for conventional foods or dietary supplements, should be aware of two provisions of the FD&C Act that, depending on the circumstances, may restrict the marketing of products containing substances that have been the subject of “substantial clinical investigations” whose existence has been made public. Section 301(ll) of the FD&C Act (21 U.S.C. 331(ll)) prohibits the marketing of any food to which has been added a drug or biologic for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless the drug or biologic was marketed in food before any substantial clinical investigations involving the drug or biologic were instituted or one of the other exceptions in section 301(ll) applies. Section 201(ff)(3)(B)(ii) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)(ii)) excludes from the dietary supplement definition any article authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless the article was marketed as a dietary supplement or as a conventional food before the IND became effective.^{xxiv} FDA interprets “authorized for investigation” to mean that the article is the subject of an IND that has gone into effect (see 21 CFR 312.40). Marketing the substance of interest “as a dietary supplement or as a food” (under section 201(ff)) or “in food” (under section 301(ll)) before seeking an IND or beginning any clinical investigations preserves the option to continue to market the substance in those forms after substantial clinical investigations have been instituted and their existence has been made public.

1. Dietary Supplements

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), a *dietary supplement* is defined, in part, as a product taken by mouth that is intended to supplement the diet and that contains one or more dietary ingredients.^{xxv} The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances

^{xxiv} FDA can create an exception to the exclusion by regulation, but only if the Agency finds that the use of the article in dietary supplements would be lawful. To date, no such regulations have been issued. The appropriate mechanism to request such a regulation is to file a citizen petition under 21 CFR 10.30.

^{xxv} See section 201(ff) of the FD&C Act (21 U.S.C. 321(ff)).

intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. Dietary supplements can be found in many forms such as tablets, capsules, softgels, liquids, or powders.

Under DSHEA, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Similarly, whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required.

However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease,^{xxvi} an IND is required under part 312. For example, a clinical investigation designed to study the relationship between a dietary supplement's effect on normal structure or function in humans (e.g., guarana and maximal oxygen uptake) or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function (e.g., fiber and bowel regularity) would not need to be conducted under an IND. However, a clinical investigation designed to evaluate a dietary supplement's ability to prevent osteoporosis or to treat chronic diarrhea or constipation would need to be conducted under an IND.

2. *Conventional Food*

Section 201(f) of the FD&C Act (21 U.S.C. 321(f)) defines a *food* as “(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.” For studies intended to evaluate the effects of a food, the analysis for whether an IND is needed turns on the intent of the clinical investigation.

As is the case for a dietary supplement, a food is considered to be a drug if it is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease,”^{xxvii} except that a food may bear an authorized health claim about reducing the risk of a disease without becoming a drug (see section VI.D.3). Therefore, a clinical investigation intended to evaluate the effect of a food on a disease would require an IND under part 312. For example, a clinical

^{xxvi} For purposes of the dietary supplement labeling requirements, a “‘disease’ is damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition” (21 CFR 101.93(g)(1)).

^{xxvii} 21 U.S.C. 321(g)(1)(B).

investigation intended to evaluate the effect of a food on the signs and symptoms of Crohn's disease would require an IND.

The following paragraph in brackets [] is STAYED.

[The FD&C Act also defines *drug* to include “articles (other than food) intended to affect the structure or any function of the body.”^{xxviii} This provision contains a parenthetical exception for foods that affect the structure and function of the body by virtue of providing nutrition to sustain life and health. Consistent with case law interpreting the “other than food” exception as applying to articles consumed primarily for taste, aroma, or nutritive value, FDA regulates conventional foods (including infant formula) that are intended to affect the structure or function of the body as foods, not drugs, as long as the intended structure or function effect derives from the product's character as a food — its taste, aroma, or nutritive value.^{xxix} However, if an edible product that might otherwise be a conventional food is intended for a use other than providing taste, aroma, or nutritive value, such as blocking the absorption of carbohydrates in the gut, the product becomes a drug because the primary purpose of consuming it has changed. In other words, the product is no longer being consumed as a food — primarily for taste, aroma, or nutritive value — but used as a drug for some other physiological effect. Accordingly, a clinical investigation intended only to evaluate the nutritional effects of a food (including medical foods^{xxx}) would not require an IND, but an investigation intended to evaluate other effects of a food on the structure or function of the body would. For example, a study of the effect of iron on hemoglobin levels in which subjects were fed beef or lamb as a source of iron would not require an IND, but a study of the effect of soy isoflavones on bone metabolism would. Similarly, a study of the ability of an infant formula to support growth of infants or of other nutritional properties of the formula would not require an IND. However, a study of other effects of the formula on the structure or function of the body (e.g., an investigation of the effects of docosahexaenoic acid in infant formula on visual acuity of infants) would require an IND.]

A clinical study intended to evaluate the safety of a food ingredient generally does not require an IND, even if the ingredient is known to have an effect on the structure and function of the body that is in addition to its taste, aroma, or nutritional effect. For example, a study of the safety of a flavor ingredient that has been found to bind to a receptor outside of the target location in the mouth would not require an IND if the intent of the study was to evaluate the safety of the ingredient when ingested as food. ***The following sentence in brackets [] is***

^{xxviii} 21 U.S.C. 321(g)(1)(C).

^{xxix} See *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir. 1983).

^{xxx} A medical food is “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” 21 U.S.C. 360ee(b)(3).

STAYED. [In contrast, if the intent of the study was to evaluate the beneficial effects (beyond nutritional effects) of binding the newly found receptor, the study would require an IND.] Similarly, a clinical study may be performed to evaluate the tolerability of a food in a specific susceptible population, including individuals with a disease. In such an evaluation, biological parameters affected by the disease may need to be assessed in order to establish tolerance. For example, the administration of high intensity sweeteners to diabetic patients to establish no adverse effect on HbA1c levels or the administration of a novel food protein ingredient to a potentially allergic population to establish lack of allergic reactivity in this population would not require an IND. However, if the intent of the study was to demonstrate an effect of the food in decreasing HbA1c levels in diabetic patients or an effect of the food to desensitize or raise threshold levels of allergic reactivity in sensitive individuals, the study would require an IND.

Consistent with the considerations for conventional foods described in the previous paragraph, an investigation intended to evaluate the effects of a medical food on a disease would require an IND. However, if the medical food is simply being fed to subjects for nutritional purposes during a study examining the effects of another intervention, the use of the medical food in the study would not trigger the need for an IND, although the study might require an IND or investigational device exemption (IDE) for the intervention being studied.

3. *Studies Intended to Support a Health Claim*

NOTE: The stay does not apply to clinical investigations intended to evaluate whether a food substance may reduce the risk of a disease in individuals less than 12 months of age, those with altered immune systems, and those with serious or life-threatening medical conditions. This subsection is in effect for such clinical investigations.

The following paragraph in brackets [] is STAYED, except as noted above.

[Section 201(g) of the FD&C Act provides that a health claim in the label or labeling of a food (conventional food or dietary supplement) characterizing the relationship between a substance (food or food component) and a disease or health-related condition does not cause the food to be a drug on the basis of that claim, provided the claim is authorized under and made in accordance with the requirements of section 403(r)(1)(B) and (r)(3) of the FD&C Act²² (for conventional foods) or under section 403(r)(1)(B) and (r)(5)(D) (for dietary supplements). Notwithstanding this provision, however, a clinical study designed to evaluate the relationship between a food substance and a disease and intended to provide support for such a claim is required to be conducted under an IND (21 CFR part 312), unless the substance-disease relationship

being studied is already the subject of an authorized health claim. Section 201(g) provides, in effect, an exemption from the normal operation of the drug definition — it permits the use of health claims that would, without the exemption, cause a conventional food or dietary supplement to be a drug. However, the exemption does not apply until the health claim has been authorized by FDA. Therefore, a study conducted to support a new or expanded health claim would require an IND. For example, a study designed to evaluate whether vitamin D may reduce the risk of one or more site-specific cancers would require an IND, as there is currently no authorized health claim for this substance-disease relationship. Similarly, a study conducted to support a petition to amend the health claim for soluble fiber from certain foods and reduced risk of coronary heart disease (21 CFR 101.81) to include a new type of fiber would require an IND.]

E. Research With Noncommercial Intent

Some believe that the IND regulations do not apply to clinical investigations that are not intended to investigate a drug's potential for commercial sale. Whether the IND regulations apply to a planned clinical investigation does not depend on whether the intent of the clinical investigation is commercial or noncommercial. Therefore, these types of studies would require an IND under part 312, unless they meet the criteria for an exemption in §§ 312.2(b) or 320.31(b) (see section IV) or the criteria in § 361.1, or the compound used is labeled with a cold isotope and used in the manner described in section V.

VII. FREQUENTLY ASKED QUESTIONS

1. *Do I need an IND if I use a lawfully marketed drug for an unlabeled indication?*

If you are a health care provider and you prescribe a marketed drug to treat a patient for an unlabeled indication (also referred to as *off-label* use), an IND is not required because this use is considered to be within the scope of medical practice and not a clinical investigation. However, if you use the marketed drug for the same purpose in a clinical investigation intended to evaluate the drug's ability to treat a disease or condition, an IND is required under part 312 unless the clinical investigation meets the criteria for an exemption for studies of lawfully marketed drugs (see 21 CFR 312.2(b) and section IV.A of this guidance).

2. *If a drug marketed for use in adults is studied in an investigator-initiated, single-center study involving children, is an IND needed?*

An IND is required under part 312 unless the clinical investigation meets the criteria for an exemption in § 312.2(b) (see section IV.A). The criterion of most importance for the exemption in this situation is whether the change in study population from adult to pediatric, or any other condition of use in the study, would significantly increase the risks (or decrease the acceptability of the risks) associated with the use of the drug (21 CFR 312.2(b)(1)(iii)). Whether risk would be significantly increased would depend on a variety of factors, including, for example, the age of the pediatric population being studied, the extent of prior pediatric experience with the drug in clinical studies or clinical practice, the amount of information available to support dosing in the study population, and the overall toxicity profile of the drug.

3. *There are drugs on the market that have not been approved by FDA. Do clinical investigations using those drugs need an IND?*

There are certain currently marketed drug ingredients that were first marketed before Congress passed the FD&C Act of 1938 (requiring demonstration of safety before marketing) or before it passed the 1962 amendments to the FD&C Act (requiring demonstration of effectiveness and safety before marketing). Sponsors of clinical investigations that use products with these ingredients should consult with FDA to determine whether the ingredient is lawfully marketed.^{xxxii} If the ingredient is not lawfully marketed, an IND is required under part 312.

4. *Can I do research on radiolabeled endogenous peptides, such as neuropeptides, without an IND?*

If the research is intended to obtain basic information about the metabolism of the peptide or its role in physiology, pathophysiology, and biochemistry, and the criteria in 21 CFR 361.1 are met (i.e., among other things, the dose of endogenous peptide to be administered is known not to cause a clinically detectable pharmacologic effect in humans), an IND is not required (see the RDRC guidance). However, if the study hypothesis concerns the diagnosis, cure, mitigation, treatment, or prevention of a disease in patients, or the criteria in § 361.1 are otherwise not met, an IND is required under part 312.

5. *Do clinical investigations of positron emission tomography (PET) drugs need INDs?*

An IND generally would be required for a PET drug investigation, unless the investigation meets the criteria in 21 CFR 361.1. To meet these criteria, the research must be intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively

^{xxxii} Ordinarily, such inquiries would be directed to CDER, Office of Compliance, Office of Unapproved Drugs & Labeling Compliance.

labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial) (21 CFR 361.1(a)).

6. *If a complementary or an alternative medicine that was derived from organic materials from a botanical source (e.g., broccoli, sprouts) is administered to subjects to study cancer prevention, is an IND required?*

A clinical investigation of a complementary or an alternative medicine derived from organic materials that is intended to evaluate the medicine's ability to diagnose, cure, mitigate, treat, or prevent disease requires an IND under part 312.^{xxxii}

7. *Is an IND required if a product containing attenuated microorganisms is evaluated for amelioration of symptoms of a disease or prevention of the disease?*

Even when a microorganism is attenuated with the intention to increase safety of a product, a clinical investigation that evaluates the potential for that microorganism to relieve symptoms of a disease or prevent the disease requires an IND under part 312, unless the study meets the criteria for an exemption under 21 CFR 312.2(b).

8. *If a product containing substances generally recognized as safe (GRAS) for use in food is administered to subjects in a study intended to evaluate the effect of the substance on the pathogenesis of a human disease, is an IND required?*

Substances designated as GRAS for use in food are generally not approved as drug products. A clinical investigation of a GRAS substance that is intended to evaluate the product's ability to diagnose, cure, mitigate, treat, or prevent disease requires an IND under part 312, unless the substance to be studied is also a lawfully marketed drug and the clinical investigation meets the criteria for exemption under 21 CFR 312.2(b).

9. *For purposes of the exemption from the IND requirements for studies using radioisotopes and FDA's exercise of enforcement discretion for studies using cold isotopes, what support is needed to determine that the labeled drug does not have a clinically detectable pharmacological effect?*

There is no requirement for a formal dose-response study to define the lower threshold for a clinically detectable pharmacological effect, and, in some cases, a study may not be needed. For example, if the labeled drug is an endogenous

^{xxxii} See the guidance for industry on *Botanical Drug Products*.

compound and the circulating blood levels or excretion rates of the endogenously produced substance are well known, there could be a basis to conclude that some small fraction of these levels or rates of administration (e.g., administration over a given interval of a very low percentage of the amount of a substance that is produced endogenously during the same interval) represents an amount without detectable pharmacological effect. Similarly, if large amounts of a substance such as an amino acid or a sugar are regularly consumed as foodstuffs, it may be possible to conclude that consumption of a small amount of these substances (e.g., a small percentage of the amount usually consumed during a meal), at least by the oral route, would be without detectable pharmacological activity (also see footnote 11).

10. Do I need an IND if my study uses a home-made version of a lawfully marketed drug?

Some investigators, or research pharmacies affiliated with the institution in which an investigator is conducting a study, compound their own versions of lawfully marketed drug products for use in clinical studies. For example, FDA is aware of instances in which the methacholine used in respiratory studies for challenge purposes has been prepared locally from raw materials obtained from a chemical supply company. Studies that use a drug product that is prepared from raw materials in place of the approved, finished product marketed by the manufacturer must be conducted under an IND (21 CFR part 312). These studies cannot meet the criteria for an exemption from the IND requirements for marketed drugs (§ 312.2(b)) because the drug product manufactured by the investigator or research pharmacy is not considered to be the lawfully marketed drug.

11. Do I need an IND if my study enrolls only a small number of subjects?

The number of subjects enrolled has no bearing on whether the study is subject to the IND regulations. The definition of *clinical investigation* specifically includes studies with as few as one subject (see section III.B).

12. Do I need an IND if my study enrolls only healthy volunteers?

The clinical condition of study subjects (e.g., the presence or absence of disease) has no bearing on whether the study is subject to the IND requirements in part 312. The definition of *clinical investigation* refers only to subjects involved in an experiment. It makes no distinction between healthy subjects or those with a disease (see section III.B).

VIII. PROCESS FOR ADDRESSING INQUIRIES CONCERNING THE APPLICATION OF THE IND REQUIREMENTS

The sponsor (or sponsor-investigator of an individual investigator-initiated study) should, in most cases, be able to determine whether the IND regulations apply to a planned clinical investigation as required under 21 CFR 312.2(a). If a sponsor is uncertain, however, we recommend that the sponsor contact the appropriate review division (i.e., for the therapeutic area being studied) in the appropriate FDA center for advice about whether the IND regulations apply (21 CFR 312.2(e)). For products regulated by CDER, an inquiry concerning the application of the IND regulations should be directed to the Chief, Project Management Staff, in the appropriate CDER review division. For products regulated by CBER, the inquiry should be directed to the applications division of the appropriate review Office.

- Organizational charts listing the CDER review divisions and their telephone numbers are available on the Internet at <http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135674.htm>.
- Organizational charts listing the CBER review divisions and their telephone numbers are available on the Internet at <http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135943.htm>.
- If the relevant review division is not known, we recommend the sponsor contact CDER's Division of Drug Information (druginfo@fda.hhs.gov) or CBER's Division of Manufacturer's Assistance and Training (matt@cber.fda.gov), Office of Communication, Outreach and Development (both addresses and telephone numbers are provided on the second title page of this guidance).

FDA will categorize inquiries concerning the application of the IND regulations as either informal or formal based on the following factors:

- The medium in which the inquiry is received
- The relative complexity of the inquiry
- The type of response requested by the inquirer or given by FDA

Informal inquiries have the following features:

- They can be communicated either orally or in writing (written communication includes email, fax, or other written correspondence).
- They pose only relatively uncomplicated questions about a planned clinical investigation that FDA can answer based on somewhat limited information.
- The inquirer is not seeking a formal written response.

In response to an inquiry intended to be informal, FDA can (1) provide an informal (qualified, nonbinding) response, either orally or in writing, concerning the applicability of the IND regulations based on its understanding of the planned clinical investigation; (2) ask for additional information before providing an informal response; or (3) determine that the inquiry poses a complex question that should be submitted as a formal inquiry. FDA will not retain and track informal responses to inquiries concerning the applicability of the IND regulations to planned clinical investigations.

Formal inquiries have all of the following features:

- They are in writing (can be paper or electronic).
- They pose a question of any level of complexity.
- The inquirer is seeking a formal written response or FDA determines that a formal written response should be given (i.e., that the inquiry cannot be answered informally).
- The documentation contains enough detail to permit FDA to provide a formal response concerning the applicability of the IND regulations to a planned clinical investigation (e.g., a study protocol, information about the drug product).

In response to a formal inquiry, FDA may provide a formal written response concerning the application of the IND requirements to a planned clinical investigation or may determine that it has insufficient information to provide a formal response and seek additional information before providing a response. The scope of any formal response would be limited to the conduct of a clinical investigation consistent with the investigation described in documentation provided to FDA. If there are significant changes to the protocol or other aspects of the planned investigation after FDA has provided a response, that response may no longer be valid. FDA will archive formal inquiries and FDA responses to those inquiries.

APPENDIX

Other Guidances that May Be Relevant to Questions Concerning the Application of the IND Requirements

FDA has issued guidances in related areas. Interested persons may wish to refer to the following documents, available on the Internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>:

- Guidance for industry on *Botanical Drug Products*, which includes guidance on submitting INDs for botanical drug products, including those botanical products currently lawfully marketed as foods (including conventional foods and dietary supplements) in the United States.
- Guidance for industry, investigators, and reviewers on *Exploratory IND Studies*, which is intended to clarify what preclinical and clinical approaches, as well as chemistry, manufacturing, and controls information, should be considered when planning exploratory studies in humans, including studies of closely related drugs or therapeutic biological products, under an IND.
- Guidance for industry on *CGMP for Phase 1 Investigational Drugs*.
- Guidance for industry and researchers on *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application*, which is intended to clarify whether research using a radioactive drug must be conducted under an IND (21 CFR part 312), may be exempt from IND requirements (21 CFR 312.2(b)), or if certain conditions are met, can be conducted under the supervision and approval of an FDA-approved Radioactive Drug Research Committee (21 CFR 361.1) without an IND. In addition, FDA has established a Web site at <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Oncology/default.htm> for easy access to information by IRBs, clinical investigators, sponsors, and others.
- Guidance for industry and FDA staff on *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions*, which is intended to clarify for sponsors how they can demonstrate compliance with the requirements of 21 CFR 312.120, as well as provide recommendations for the submission of information, whether in an IND or application for marketing approval for a drug or biological drug product, to demonstrate that a non-IND foreign clinical study was conducted in accordance with GCP.
- Guidance on *Emergency Use Authorization of Medical Products*, which is intended to inform industry, government agencies, and FDA staff of the Agency's general recommendations and procedures for issuance of Emergency Use Authorizations (EUAs).

Appendix 10: Georgia Tech Regulatory Affairs Office ClinicalTrials.gov Initial Questions Document

ClinicalTrials.gov allows the registration of trials that:

- 1) are required to register under FDAAA 801 and the Final Rule (42 CFR part 11); or,
- 2) are funded by the NIH and qualify as a clinical trial under the NIH definition

NIH Definition of a Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

ClinicalTrials.gov database requirements

General Instructions: Please do not use any pronouns, as your submission will not be accepted. For example, please change “we” to “the investigators” and “you” to “participants.”

Study Identification

Unique Protocol ID (GT protocol number):

Brief Title (lay language, must be sufficiently descriptive):

Acronym (if any):

Official Title:

Secondary IDs (NIH grant or Contract Award Number):

Study Type: [Select one] Interventional / Observational / Patient Registry / Expanded Access

Study Status

Record Verification Date:

Overall Recruitment Status: [Select one]

Recruiting / Enrolling by invitation / active, not yet recruiting /

Complete/Suspended / Terminated (halted permanently) / Withdrawn (no participants enrolled)

Study Start Date: MM/DD/YYYY [Select one] Actual / Anticipated

Primary Completion Date: MM/DD/YYYY [Select one] Actual / Anticipated

Study Completion Date: MM/DD/YYYY [Select one] Actual / Anticipated

Sponsor/Collaborators

Responsible Party: [Select one] Sponsor (Georgia Tech) / Sponsor-Investigator (PI)

[Click Here to Go to the Table of Contents](#)

Sponsor: Georgia Institute of Technology

Collaborators:

Oversight

U.S. FDA-regulated Drug: [Select one] Yes / No

U.S. FDA-regulated Device: [Select one] Yes / No

U.S. FDA IND/IDE: [Select one] Yes / No

Human Subjects Protection Review:

Board Status:

Approval Number:

Board Name: : Georgia Institute of Technology Central IRB

Board Affiliation: Georgia Institute of Technology

Phone:

Email: irb@gatech.edu

Address:

Office of Research Integrity Assurance

Georgia Institute of Technology

Dalney Street Building

926 Dalney Street NW, Atlanta, GA 30332-4025

Data Monitoring Committee: [Select one] Yes / No

FDA Regulated Intervention: [Select one] Yes / No

Study Description

Please do not use any pronouns, as your submission will not be accepted. For example, please change “we” to “the investigators” and “you” to “participants.”

Brief Summary (lay language):

Detailed Description:

Conditions

Conditions or Focus of Study (you must select these from the following database:

<https://meshb.nlm.nih.gov/search>):

Keywords:

Study Design

[Click Here to Go to the Table of Contents](#)

This section varies on the type of study. Therefore, after you provide the information requested in this form, we will then follow-up to ask the variable questions that are presented in this section (please see either [Observational Supplemental Questions](#) document or [Investigational Supplemental Questions](#) document).

Outcome Measures

Instructions: Please ensure that each outcome measure only describes one unit of measure, such as weight or height. Assessments with different Units of Measure must be presented in separate Outcome Measures.

Instructions: Please ensure that the outcome measure explicitly include the NAME OF THE MEASUREMENT and/or MEASUREMENT TOOL used to assess the measure. Please specify the measurement (e.g. "Incidence of...", "Rate of...", "Concentration of...", "% of patients with...", etc.) and the measurement tool (e.g., descriptive name of scale, physiological parameter, questionnaire, etc.) that will be used to assess this outcome measure.

Primary Outcome Measure(s):

Outcome 1:

Title:

Description:

Time Frame:

(Add additional Primary Outcome if needed)

Secondary Outcome Measure(s) (If Any):

Outcome 1:

Title:

Description:

Time Frame:

(Add additional Secondary Outcome if needed)

Other Pre-specified Outcomes (If Any):

Eligibility

Sex: [Select one] All / Male / Female

[Click Here to Go to the Table of Contents](#)

Gender Based: [Select one] Yes / No

Age Limits:

Minimum Age:

Maximum Age:

Accepts Healthy Volunteers: [Select one] Yes / No

Eligibility Criteria:

Inclusion Criteria:

Exclusion Criteria:

Contacts/Locations

Overall Contacts:

Central Contact Person:

First Name: MI: Last Name: Degree:

Phone: Ext. Email:

Central Contact Backup:

First Name: MI: Last Name: Degree:

Phone: Ext. Email:

Overall Study Officials:

First Name: MI: Last Name: Degree:

Organizational Affiliation:

Official's Role: [Select one] Study Principal Investigator / Study Chair /
Study Director

(Add any additional Study Officials if needed)

Locations:

Facility:

Name: (Lab)

City:

State/Province: ZIP/Postal Code:

Country:

Site Recruitment Status: [Select one]

Recruiting / Enrolling by invitation / active, not yet recruiting / Complete /Suspended / Terminated (halted permanently) / Withdrawn (no participants enrolled)

Facility Contact:

First Name: MI: Last Name: Degree:

Phone: Ext. Email:

Facility Contact Backup: (if applicable)

First Name: MI: Last Name: Degree:

Phone: Ext. Email:

Investigators:

First Name: MI: Last Name: Degree:

Role: [Select one] Site Principal Investigator / Site Sub-Investigator

(Add Additional Investigators if applicable)

IPD Sharing Statement

Plan to Share IPD: [Select one] Yes / No / Undecided

Plan Description: (if applicable)

References

Citations:

Links:

Available IPD/Information: (References to de-identified individual participant data (IPD) sets and supporting information)

Document Section

Only certain studies need to have study documents uploaded.

- *Full study protocol and statistical analysis plan -- required with results information submission for studies with a Primary Completion Date on or after January 18, 2017*
- *Informed consent forms - optional for all studies*

Upload as PDF/A Documents

Results Section *Results submission is required by FDAAA 801 for certain [applicable clinical trials](#) of drugs, biologics and devices. Note: other clinical trials may need to have results submitted based on other funder or sponsor policies.*

[Record must have a ClinicalTrials.gov ID (NCT number) before results can be entered.]

[Delay Results](#) *For applicable clinical trials subject to FDAAA 801, results submission may be delayed (in limited circumstances) with a Certification or Extension Request.*

**Appendix 11: Georgia Tech Regulatory Affairs Office ClinicalTrials.gov
Investigational Questions Document**

Study Design

Primary Purpose: [Select one]

Treatment / Prevention / Diagnostic / Supportive Care / Screening / Health
Services Research / Basic Science / Device Feasibility / Other

Study Phase: [Select one]

N/A / Early Phase 1 / Phase 1 / Phase 1 and 2 / Phase 2 / Phase 2 and 3 / Phase 3 /
Phase 4

Interventional Study Model: [Select one]

Single Group / Parallel / Crossover / Factorial / Sequential

Model Description:

Number of Arms:

Masking: [Select all that apply]

Participant / Care Provider / Investigator / Outcomes Assessor / None (Open
Label)

Masking Description:

Allocation (select N/A for single-arm studies): [Select one] N/A / Randomize / Non-
Randomized

Enrollment: #___ [Select one] Anticipated / Actual

Arms and Interventions

Arms:

Arm Title:

Arm Type: [Select one]

Experimental / Active Comparator / Placebo Comparator / Sham
Comparator / No intervention / Other

Arm Description:

Add any additional arms by repeating the information above.

Interventions

Intervention Type: [Select One]

Drug / Device / Biological/Vaccine / Procedure/Surgery / Radiation /
Behavioral / Dietary Supplement / / Genetic / Combination Product /
Diagnostic Test / Other

Intervention Name:

Other Intervention Names (if any):

Intervention Description:

Add any additional arms by repeating the information above.

Appendix 12: Georgia Tech Regulatory Affairs Office ClinicalTrials.gov Observational Questions Document

Study Design

Observational Study Model: [Select one]

Cohort / Case-Control / Case-Only / Case-Crossover / Ecologic or Community /
Family Based / Other

Time Perspective: [Select one]

Retrospective / Prospective / Cross-Sectional / /Other

Biospecimen Retention: [Select one]

None Retained / Samples with DNA / Samples without DNA

Enrollment: #___ [Select one] Anticipated / Actual

Number of Groups/Cohorts: #___

Groups and Interventions

Groups

Group/Cohort Label:

Instructions: Brief, descriptive label to be used as row or column heading
in tables.

Group/Cohort Description:

Instructions: Describe the intervention(s) to be administered. For drugs use
generic name and include dosage form, dosage, frequency and duration.

Add any additional arms by repeating the information above

Interventions/Exposures:

Intervention Type: [Select one]

Drug / Device / Biological/Vaccine / Procedure/Surgery / Radiation /
Behavioral / Dietary Supplement / / Genetic / Combination Product /
Diagnostic Test / Other

Other Intervention Names (if any):

Instructions: Include brand names, serial numbers and code names to improve search results on the ClinicalTrials.gov web site.

Add any additional intervention names if needed.

Intervention Description:

Instructions: Do not repeat information already included in arm/group descriptions.

Add any additional intervention names if needed.

Cross Reference:

Instructions: This section is depicted as a matrix within clinicaltrials.gov. Therefore, please list which groups will receive which interventions during this study.

Georgia Institute of Technology
Regulatory Affairs and Clinical Trials
POLICIES & PROCEDURES

GLOSSARY

Revised: July 2022

Adverse events:

1. An Adverse Event is an unfavorable event associated with the study interventions. Such events may be anticipated or unanticipated. An adverse event includes adverse drug experiences, adverse device effects, and problems involving harm to human subjects. (For example, adverse events include allergic reaction, hospitalization, supply problems with protocol-specific materials, or theft of a laptop computer that contains study identifiers, etc.).
2. A Serious Adverse Event is one that is fatal, life-threatening, persistent, significantly disabling or incapacitating, requires inpatient hospitalization or prolongation of hospitalization, results in congenital anomaly or defect, and/or that is a significant medical incident. (A significant medical incident is considered a serious, study-related adverse event because, it may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)
3. An Unanticipated Adverse Event is one that results from a study intervention and was not expected or anticipated from prior experience. An Unanticipated Adverse Event can include expected adverse events that occur with greater frequency or severity than predicted from prior experience. It is possible for an adverse event to be characterized as serious and unanticipated.

Anonymous Samples: specimens lacking any code or identifier that would allow a link back to the subject who provided it.

Applicable Clinical Trial (ACT): Under Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801), the United States Congress defined an “Applicable Clinical Trial” as an applicable device clinical trial or an applicable drug clinical trial (both listed below). These terms became codified at section 402(j) of the Public Health Service (PHS) Act, and include conforming amendments to the Federal Food, Drug, and Cosmetic FD&C Act (FD&C Act).

Applicable Device Clinical Trial: The term ‘applicable device clinical trial’ means:

- i a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the

- Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and
- ii a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
 - a. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 904 (2007).

Applicable Drug Clinical Trial: The term ‘applicable drug clinical trial’ means a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act.

- i “Clinical Investigation”: For purposes of subclause (I), the term ‘clinical investigation’ has the meaning given that term in section 312.3 of title 21, Code of Federal Regulations (or any successor regulation).
- ii “Phase I”: For purposes of subclause (I), the term ‘phase I’ has the meaning given that term in section 312.21 of title 21, Code of Federal Regulations (or any successor regulation).

Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 904 (2007).

Authorization: Authorization is the HIPAA equivalent of consent to use and disclose data.

Case Report Form: A record of data collected about each participant in a clinical trial; data are used by sponsor or sponsor-investigator to test hypothesis or to answer research question.

Clinical Investigation: Under §42 CFR 11, a “Clinical Study” is defined as “research according to a protocol involving one or more human subjects to evaluate biomedical or health-related outcomes, including interventional studies and observational studies..” This terms is interchangeable with “Clinical Investigation” and “Clinical Research.”

Clinical Trial:

- As Defined by the FDA (also see “Applicable Clinical Trial”): Under Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801), the United States Congress defined an “Applicable Clinical Trial” as an applicable device clinical trial or an applicable drug clinical trial (both listed below). These terms became codified at section 402(j) of the Public Health Service (PHS) Act, and include conforming amendments to the Federal Food, Drug, and Cosmetic FD&C Act (FD&C Act).

- As Defined by NIH: NIH defines a clinical trial as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. (See NOT-OD-15-015: <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html>).
- Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.
- As Defined by OHRP: Under §42 CFR 11, a “Clinical Trial” is defined as “a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no intervention) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes.”

Combination Product: A product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product.

Co-Principal Investigator: Individuals who share the responsibility for the study with the Principal Investigator and therefore requires the same qualifications as for PI.

Co-Investigator: This title designates key personnel for a project, but without the oversight responsibility of a Principal Investigator.

Consideration: Value exchanged to create a contract.

Covered Entity: Covered entities are health care providers, health plans, and health care clearinghouses.

Data and Safety Monitoring Board (DSMB): Also called a “Data Monitoring Committee” (DMC), a DSMB is an independent committee that conducts ongoing review of data to assure subject safety.

Data Safety Monitoring Plan: A plan written to ensure that the relevant data are collected and assessed to monitor subject safety within a study. Part of the DSMP may be the establishment of a Data and Safety Monitoring Board, but is not necessarily required for every DSMP.

Data Use Agreement: The official agreement between the provider and recipient of Protected Health Information (PHI) collected under a protocol. The

[Click Here to Go to the Table of Contents](#)

agreement defines the PHI, states whether it qualifies as a Limited Data Set, and names the persons (or positions) authorized to have access to the Protected Health Information collected in the study. Other terms and conditions may apply.

Experimental Subject: The Department of Defense definition is: An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction [32CFR.210.102 (f) reference (c)]. Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose.

Genetic Research: any research involving the analysis of human DNA and chromosomes as well as biochemical analysis of proteins and metabolites when the intent of the research is to collect and evaluate information about heritable disease and/or characteristics within a family.

Guardian: An individual authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. Can also be an individual who is authorized to consent on behalf of a child to participate in research. **NOTE:** In 2013, the Food and Drug Administration revised its definition of *Guardian* at 21 CFR 50.3(s) as follows: "*Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.*"

HIPAA: Health Insurance Portability and Accountability Act (HIPAA): The Department of Health and Human Services' *National Standards to Protect the Privacy of Personal Health Information* are promulgated in the Health Insurance Portability and Accountability Act (HIPAA), commonly referred to as the "Privacy Act." This Act specifies requirements for protection of individually identifiable health information, or "protected health information" (PHI).

Human Subject: A *human subject* is a living individual about whom an investigator conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. Included in the definition of human subject are human embryos, fetuses, and any human tissue or fluids. Thus, the scope of *human subject* is interpreted broadly. If you are interviewing people, looking at medical records or conducting a survey, you are involving human subjects in your research. [See](#)

[Appendix 3 for an important distinction in this definition for research involving DOD.](#)

Hybrid Entity: An organization where some parts are subject to HIPAA, while others are not. In such cases, the Privacy Rule applies only to specified units.

Identifiable/Coded Samples: specimens that can be linked back to the subject who provided them.

Identifier: Information that links specimens or data to individually identifiable living people or their medical information. Examples include names, social security numbers, medical record numbers, and pathology accession numbers.

Legally Authorized Representative: 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.

Principal Investigator: The individual responsible for the conduct of the study.

Prospective Collection: specimens do not exist 'on the shelf' when request is made to Georgia Institute of Technology IRB for approval.

Protected Health Information (PHI): Protected health information includes all *individually identifiable* health information transmitted or maintained by an organization covered by the HIPAA regulations (a "covered entity"), regardless of form. Specifically, if it is Individually Identifiable Health Information (IIHI) that is:

- created or received by a health care provider, health plan, employer, or health care clearinghouse; and
- personal health information that relates to:
 - the past, present, or future physical or mental condition,
 - the past, present, or future provision of care to an individual, or
 - the past, present or future payment for provision of health care to an individual, and identifies the individual (or there is a reasonable basis to believe that the information can be used to identify the individual).

Retrospective Collection: proposed research involves using specimens that already exist, i.e., already collected and are 'on the shelf', stored or frozen at time of protocol submission to Georgia Institute of Technology IRB.

Sponsor: 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.

Sponsor-investigator: 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.

Test article: 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).

Third Party: Refers to tissue that is not obtained from the human subject directly, but via another source, i.e., tissue bank, Department of Pathology etc. The third party may have the tissue coded with respect to subject identity, but the investigator receives the tissue in an anonymous manner, i.e., no way to link the subject's identity to the tissue once it is in the investigator's hands.