1. Applicability

FDA regulations apply to all clinical investigations that propose to introduce drugs, biologics or devices to subjects within the United States or that propose to deliver drugs, biologics or devices to subjects for introduction into United States interstate commerce.

2. Definitions

2.1. Clinical investigation

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 (FDA) under the Federal Food, Drug and Cosmetic Act (the Act), or is not subject to requirements for prior submission to the FDA under the Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

2.2. Clinical trial (definition to be used for specific purposes delineated in Section 6 below *only*)

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

2.3. Human subject

An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

2.4. Investigational device

A device, including a transitional device that is the object of an investigation.

2.5. Investigational new drug

A new drug or biological drug that is used in a clinical investigation; the term also includes a biological product that is used in vitro for diagnostic purposes.

2.6. Minimal risk

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

2.7. Noninvasive

A diagnostic device or procedure that does not by design or intention: a) penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra; or b) enter the ear beyond the external auditory canal, the nose beyond the

nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os.

(k) *Noninvasive,* when applied to a diagnostic device or procedure, means one that does not by design or intention: (1) Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or (2) enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.

Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.

2.8. Significant risk device

An investigational device that: a) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; b) 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; c) 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 d) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

2.9. 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.

2.10. 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.

2.11. 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 FDA regulations.

3. Principal Investigator (PI) Responsibilities

The PI of a clinical investigation is responsible for the following:

3.1. Ensuring that the test article is used in accordance with the IRB approved protocol.

3.2. Ensuring that only authorized individuals have access to and use the test article.

3.3. Ensuring compliance with the dispensing policies of the dispensing entity.

3.4. Ensuring compliance with all applicable FDA requirements.

3.5. Maintaining clinical investigation records for the longest of:

a) A period of at least two years following the date on which the results of the clinical investigation are submitted to the FDA in support of an application for a research Investigational New Drug Number or Investigational Device Exemption or marketing permit; OR

b) A period of at least two years following the date on which an application for research or marketing permit (in support of which the results of the clinical investigation were submitted to the FDA) is approved by the FDA; OR

c) Two years after the investigation is discontinued and FDA is notified of that fact.

4. IRB Submission Requirements

When proposing a clinical investigation, the PI is responsible for submitting the following additional materials to the IRB:

4.1. For clinical investigations that require an IND, the FDA issued IND number.

4.2. For clinical investigations that require an IDE, the FDA issued IDE number.

4.3. For clinical investigations involving an investigational drug or biologic, an investigator's brochure.

4.4. For clinical investigations involving an investigational device, detailed information about the device and/or device brochure, if available.

4.5. Sponsor's protocol, where applicable.

5. Additional Elements to be Included in the Informed Consent Document

In addition to the informed consent requirements outlined in CUNY HRPP Policy: Informed Consent Process and Documentation, Informed consent documents for research involving the use of test articles must include the following:

5.1. A clear statement that the test article is investigational and has not been approved or has not been approved for the purpose being studied.

5.2. 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.

5.3. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

5.4. A statement that the FDA and/or the study sponsor may have access to identifiable subject data.

5.5. A clear description of the alternatives available to the subjects, including when applicable, access to the test article outside of the research setting.

5.6. A clear explanation of the party responsible for the cost of the test article; cost of the procedures associated with the use of the test article; and cost associated with treatment required as a result of related adverse events.

6. Posting of Clinical Trial Consent Form

For each clinical trial (as defined in 2.2 above) conducted or supported by a Federal department or agency, a copy of the IRB-approved informed consent form used to enroll subjects must be posted on a publicly available Federal website established as a repository for such informed consent forms.

6.1. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal website, such Federal department or agency may permit or require redactions to the information posted.

7. Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

The IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in Section 5 above; OR the IRB may waive the requirement to obtain informed consent when the IRB finds and documents that:

a) The clinical investigation involves no more than minimal risk, as defined in 2.6 above;
b) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
c) The clinical investigation could not practicably be carried out without the waiver or alteration; AND
d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

8. Exception from Informed Consent Requirements for Use of a Test Article (NOT including Investigational In Vitro Diagnostic Devices)

FDA allows for an exception from informed consent requirements in the following circumstances:

8.1. Before the use of the test article, both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing that:

a) The human subject is confronted by a life-threatening situation necessitating the use of the test article; AND

b) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject; AND

c) Time is not sufficient to obtain consent from the subject's legal representative; AND

d) 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.

8.1.1. PI is responsible for submitting a report related to such an event and the related independent physician evaluation to the IRB within 5 working days after the use of the article.

8.2. 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 10.1 above 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.

8.2.1. PI is responsible for submitting a report related to such an event and the related independent physician evaluation to the IRB within 5 working days after the use of the article.

9. Exception from Informed Consent Requirements for Use of Investigational In Vitro Diagnostic Devices

9.1. Before the use of investigational in vitro diagnostic devices used to identify chemical, biological, radiological, or nuclear agents, both the investigator and a physician who is not otherwise participating in the clinical investigation make the determination and later certify in writing ALL of the following:

a) 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.

b) Informed consent cannot be obtained from the subject because:

- There is 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

- Time is not sufficient to obtain consent from the subject without risking the life of the subject.

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

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

9.1.1. PI is responsible for submitting a report related to such an event and the related independent physician evaluation to the IRB and FDA within 5 working days after the use of the article.

9.2. If the use of the investigational device is, in the opinion of the investigator, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in 11.1 above 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.

9.2.1. PI is responsible for submitting a report related to such an event and the related independent physician evaluation to the IRB and FDA within 5 working days after the use of the article.

9.3. PI is responsible for disclosing the investigational status of the in vitro diagnostic device and what is known about the performance characteristics of the device in a report to the subject's health care provider and in any report to public health authorities.

9.4. PI is responsible for providing the IRB with information (as closely following the requirements of informed consent as possible) that will be provided to the subject and detailed description of the procedures that will be used to provide this information to the 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.

9.4.1. The IRB is responsible for ensuring the adequacy of the information and for ensuring that procedures are in place to provide this information to each subject or the subject's legally authorized representative.

INVESTIGATIONAL DRUGS OR BIOLOGICS

10. When is an Investigational New Drug Application (IND) to the FDA Required?

An IND is required for clinical investigations of a drug or biologic that meets ANY of the following criteria:

10.1. The clinical investigation is intended to be reported to the FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug.

10.2. For a drug that is lawfully marketed as a prescription drug product, the investigation is intended to support significant change in advertising for the product.

10.3. The investigation involves a route of administration or dosage level or use in a patient population or other factors that significantly increase the risks (or decrease the acceptability of risks) associated with the use of the drug.

10.4. The clinical investigation requires exception from informed consent requirements for emergency research in accordance with FDA regulations.

11. When is an IND Not Required?

Investigational use of drugs and biologics is exempt from FDA's requirement for obtaining an IND in the following circumstances:

11.1. The clinical investigation of a drug product that is lawfully marketed in the United States does not require an IND if ALL of the following conditions are met: a) none of the criteria in section 10 above are met; b) the investigation is conducted in compliance with IRB review requirements and informed consent requirements; and c) the investigation is conducted in compliance with FDA requirements for promotion of investigational drugs.

11.2. A clinical investigation involving an in vitro diagnostic biological product (specifically, blood grouping serum; reagent red blood cells; and anti-human globulin) IF: a) it is intended to be used in a diagnostic procedure that confirms that diagnosis made by another, medically established, diagnostic product or procedure; AND b) it is shipped in compliance with FDA requirements for drugs for investigational use in laboratory research animals or in vitro tests.

11.3. A drug intended solely for tests in vitro or in laboratory research animals is exempt from IND requirements if it is shipped in accordance with FDA requirements for drugs

for investigational use in laboratory research animals or in vitro tests.

11.4. A clinical investigation involving use of a placebo is exempt from IND requirements if the investigation does not otherwise require submission of an IND.

INVESTIGATIONAL DEVICES

12. When is an Investigational Device Exemption (IDE) from the FDA Required?

12.1. Clinical investigations of devices to determine safety and effectiveness require an IDE unless any of the conditions in section 6 below are met.

12.2. Investigation of an off-label use of a device with a 510(k), or substantially equivalent to a legally marketed device, designation by the FDA may require an IDE.

13. When is an IDE Not Required?

Investigational use of devices is exempt from FDA's requirement for obtaining an IDE in the following circumstances:

13.1. An investigation of a non-significant risk device if the IRB determines that the device is not a significant risk device and grants an approval for its described use.

13.2. A diagnostic device if the testing a) is noninvasive; b) does not require invasive sampling procedure that presents significant risk; c) does not by design or intention introduce energy into a subject; AND d) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

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

13.4. A device with a 510(k) designation does not require an IDE for use in a clinical investigation in accordance with the labeling cleared by FDA.

13.5. Other less common circumstances described in FDA regulations at 21 CFR 812.2.

EMERGENCY RESEARCH

FDA regulations allow for mechanisms by which certain types of emergency research may be conducted without the requirement for obtaining informed consent from the subject or the subject's legally authorized representative. If a CUNY researcher plans to become engaged in such research, s/he must first contact CUNY's research compliance staff for guidance on how to proceed.

HUMANITARIAN USE DEVICES (HUD)

FDA regulations require the review and approval from an IRB prior to the use of a HUD. If a CUNY researcher plans to administer a HUD, s/he must first contact CUNY's research compliance staff for guidance on how to proceed.

References:

1. Code of Federal Regulations, Title 21 – Food and Drugs:

    a. Part 50 – Protection of Human Subjects
    b. Part 56 – Institutional Review Boards
    c. Part 312 – Investigational New Drug Application
    d. Part 812 – Investigational Device Exemptions
    e. Part 814, Subpart H – Humanitarian Use Devices

2. 21st Century Cures Act (PL 114-255), Title III, Section 3024

3. US Food and Drugs Administration. *Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors.*