

**COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK**

**OFFICE OF THE
EXECUTIVE VICE PRESIDENT FOR RESEARCH**



**CLINICAL RESEARCH
HANDBOOK**

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I. INTRODUCTION

A. Purpose of Handbook

This Handbook has been created to give practical guidance to clinical research coordinators (**CRCs**) and other clinical researchers in the management of clinical research at Columbia University. It is a “how to” guide oriented specifically to clinical research conducted at Columbia. It is intended to be used in conjunction with a mandatory training course for CRCs, but it can also serve as a general reference guide for faculty, staff and students at the University who are involved in clinical research. The Handbook will help faculty, staff and students to administer clinical research in accordance with governmental regulations and University policies.

Readers should be advised that changes in policies and regulations may be more current than the contents of this Handbook. While every attempt will be made to keep this Handbook up-to-date, ultimately the most current information will be found in government regulations, sponsor documentation and the University’s numerous websites.

B. Resources

The University has websites and other resources that provide a wealth of information that may be helpful to CRCs. The following describes those that are the most relevant to persons doing clinical research.

1. Office of the Executive Vice President for Research (EVPR)

The Office of the EVPR’s website <http://evpr.columbia.edu/> provides quick links to other useful websites including:

- Human Research Protection Office/Institutional Review Boards
<http://www.cumc.columbia.edu/dept/irb/>
- Clinical Trials Office <https://cto.cumc.columbia.edu/>
- Sponsored Projects Administration <http://spa.columbia.edu/>
- Sponsored Projects Finance
<http://finance.columbia.edu/content/sponsored-projects-finance>
- Research Compliance and Training <http://www.columbia.edu/cu/compliance/>

2. Handbooks

In addition to this Handbook, the Office of the EVPR has produced the following Handbooks to provide guidance to faculty, staff and students at the University in matters relating to research. The Handbooks are available in pdf on the EVPR website.

- [Sponsored Projects Handbook](#)
- [Animal Research Handbook](#).
- [Research Radiation Safety Handbook](#).

3. Rascal

Rascal is a web-based suite of information technology (IT) modules that was developed internally at the University to house many of the University's research compliance processes. Rascal can be accessed at: <https://www.rascal.columbia.edu>.

There will be many references to Rascal in this Handbook. Currently, Rascal serves as the electronic system for the following:

Training and Certifications

Rascal houses a number of training courses and tracks compliance with training requirements. The following are the courses most relevant to clinical researchers:

- Human Subjects Protection
- Privacy and Security (HIPAA)
- Responsible Conduct of Research
- Financial Conflicts of Interest and Research
- FDA Requirements of Sponsor-Investigator Studies
- Clinical Research Coordinator Mandatory Training
- Informed Consent in Genetic Research
- Safety Training
 - Laboratory Safety, Clinical Hygiene and Hazardous Waste Management
 - Initial Radiation Safety Training
 - Annual Radiation Safety Refresher Training
 - Bloodborne Pathogens/Infection Control
 - Shipping Biological (Infectious or Potentially Infectious) Materials and Genetically Modified Microorganisms
 - Shipping with Dry Ice, Exempt Specimens and Excepted Quantities of Dangerous Goods
 - Safe Use of Formaldehyde

Human Subjects/Institutional Review Boards (IRB)

Rascal is used by investigators to create IRB protocols and informed consent documents and by the Human Research Protection Office (HRPO) to administer the protocol review process. See **Preparing for a Study: Review and Finalization of Proposals and Contracts (Chapter VI)**.

Rascal also links data from other modules that are needed to obtain IRB approval of a protocol:

- Financial Conflicts of Interest
- Training Certifications
- Hazardous Materials
 - Recombinant DNA
 - Infectious Agents
 - Human Materials or Other Potentially Infectious Materials
 - Hazardous Chemicals or Toxins
 - Radiation
 - Lasers
 - Controlled Substances

Proposal Tracking

Rascal routes electronic approvals of proposals or contracts administered by Sponsored Projects Administration (SPA). These include Principal Investigator (PI) certifications and departmental and New York-Presbyterian Hospital approvals. See **Preparing for a Study: Review and Finalization of Proposals and Contracts – Approval Process (Chapter VI, Section D)**.

Any Columbia employee who has a Columbia UNI may use Rascal. The first time you log into Rascal, you should complete a user profile and fill out an annual financial conflict of interest disclosure form. For more information on financial conflicts of interest, see **Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications – Financial Conflicts of Interest (FCOIs) (Chapter VI, Section E(1))** in the **Sponsored Projects Handbook**.

C. Annexes

This Handbook contains a number of Annexes; an Index of Annexes can be found following the text of this Handbook immediately prior to the Annexes. See **Annex A** for a Glossary of Acronyms and **Annex B** for a Glossary of Terms used in this Handbook.

D. Clinical Research

1. Definitions of Clinical Research and Clinical Trials

The most commonly used definitions of clinical research and clinical trials can be found in the NIH Grants Policy Statement (<http://grants.nih.gov/grants/glossary.htm>), where they are defined as follows:

Clinical Research:

- Patient oriented research, which is research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) in which an investigator (or colleague) directly interacts with human subjects. It includes research on mechanisms of human disease, therapeutic interventions, clinical trials and development of new technologies, but does not include in vitro studies using human tissues that cannot be linked to a living individual unless the research involves a clinical investigation of a medical device.
- Epidemiological and behavioral studies
- Outcomes research and health services research

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.

The NIH has provided the following additional definitions relating to clinical trials:

- **Research:** as defined in 45 CFR 46.102(d).
- **Human Subjects:** as defined in 45 CFR 46.102(f)
- **Prospectively Assigned:** a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo or other control) of a clinical trial.
- **Intervention:** a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. 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.
- **Health-related Biomedical or Behavioral Outcomes:** the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvements of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and positive or negative changes to quality of life.

For additional information, see <http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials>.

The Clinical Trials Office (**CTO**) has primary responsibility for administering industry sponsored clinical trials and clinical research. SPA has primary responsibility for

administering all other clinical trials and clinical research. See **Preparing for a Study: Review and Finalization of Proposals and Contracts (Chapter VI)** and **Introduction: Primary University Offices Involved in Sponsored Research: Office of the Executive Vice President for Research (EVPR) (Chapter I, Section E)** in the **Sponsored Projects Handbook** for further information on the CTO and SPA.

Although Columbia's technology transfer office, Columbia Technology Ventures (CTV), may negotiate certain industry sponsored agreements, it does not do so for any industry sponsored clinical trials or clinical research. All such agreements are processed by the CTO.

2. Sponsored Research vs. Non-Sponsored Research

Clinical research can be either sponsored or non-sponsored:

- **Sponsored research** is research funded by a source that is external to the University. The sponsor can be a government agency, a foundation, an industrial company or an individual.
- **Non-Sponsored research** is research that receives no financial support or is funded by an internal University source, such as a department.

For further information on what constitutes Sponsored Research, see **Introduction: Sponsored Projects (Chapter 1, Section D)** in the **Sponsored Projects Handbook**.

3. Clinical Research Terminology

There are two types of study designs in clinical research: experimental studies and observational studies.

Experimental Studies

In experimental studies, the PI studies the cause and effect relationship between the treatment and the outcome in groups of subjects enrolled in the study. Three of the methods of studying cause and effect are: use of a control group, randomization and blinding. These methods can be used individually or in combination.

Control Groups: A study of a new treatment or management method often uses a control group. Controls are subjects who are included in a study for comparison to the intervention/treatment group. The control group may be given no treatment, a treatment with a placebo that is not physically distinguishable from the intervention being studied or the current standard treatment. In a concurrent control study, subjects in control groups are managed in exactly the same manner as the treatment subjects. When the treated and control groups are compared, the results of the treatment can be distinguished from the act of treating.

In historical control studies, a new intervention is used for all participants and the results are compared to the outcomes in previous comparable participants.

A cross-over design is used in a control trial in which each participant serves as his/her own control. For instance, each participant will receive either the intervention or control in the first period and the alternative in the second period.

Randomization: Randomization is the process of assigning research subjects to study arms by chance. Random allocation of participants to specific treatment groups ensures that each group is, on average, as alike as possible to the other groups(s) and that each group has a similar level of risk. The most elementary form of randomization is called simple randomization represented by a toss of a coin each time a participant is eligible to be randomized. In clinical trials, randomization is usually achieved using a randomization list or through the use of an Interactive Voice Randomization System (IVRS) via the telephone or a web-based randomization system.

Some trials use stratification, a process that divides subjects into subsets or strata (i.e., age, sex or clinical history) as a way of ensuring that each stratum is represented in the sample and making treatment groups more comparable. Randomization within each stratum will result generally in proportional numbers of subjects in each treatment group within the stratum and overall.

Blinding: Blinding is the process of keeping the type of study intervention provided to subjects unknown to the subject and/or the research team. Single-blind means only the research subject does not know whether he/she is in the intervention group or the placebo group. Double-blind means neither the subject nor the research team knows. Blinded studies often use placebos (i.e., a study intervention designed to look like an active treatment, but having no active properties).

Observational Studies

In an observational study, specific events or findings within the study population are collected and studied by the researcher without research related intervention by the researcher. This type of design is usually used in investigations where it would be unnecessary, unfeasible, inappropriate or unethical to conduct an experimental study.

The following are types of observational studies:

Cohort Studies: A cohort study examines certain specific events or outcomes in a group of subjects who are followed over time. The study compares the incidence of a given event/outcome in different groups to determine whether there are associations between groups.

Case-Control Studies: A case-control study is a retrospective study comparing persons with a disease, condition or exposure to persons without the disease, condition or exposure to compare outcomes between the groups.

E. Regulatory Framework and Good Clinical Practice

CRCs should have a working knowledge of the laws, regulations and guidances relating to clinical research and the federal agencies that primarily administer them. The following is a brief outline of the most relevant federal agencies, regulations and guidances; they will not be discussed in detail here, but will be referred to throughout this Handbook as the subject requires. It is University policy that all clinical research adhere to federal regulations regardless of the funding source.

1. Federal Agencies and Regulations

The Department of Health and Human Services (**HHS**) is the federal government's principal agency for protecting the health of all Americans. HHS includes more than 300 programs covering a wide spectrum of activities. The agencies that are of particular interest in clinical research are the following:

- **Office for Human Research Protections (OHRP)** <http://www.hhs.gov/ohrp/>. OHRP has primary responsibility for the oversight of IRBs and ensuring compliance with HHS regulations for the protection of human subjects in research.
- **National Institutes of Health (NIH)** <http://www.nih.gov/>. NIH is the primary federal agency conducting and supporting biomedical research. If any clinical research is sponsored by NIH, all research personnel should be familiar with the following:
 - NIH Grants Policy Statement at <http://grants.nih.gov/policy/nihgps/index.htm>
 - NIH Guide for Grants and Contracts at <https://grants.nih.gov/funding/searchGuide>
 - See also the NIH website at <http://grants.nih.gov>.
- **Food and Drug Administration (FDA)** <http://www.fda.gov/>. The FDA has primary responsibility for the regulation of drugs, devices and biologics. The following are the principal regulations of the FDA relating to clinical research involving drugs, devices and biologics:
 - [21 CFR Part 11](#) – Electronic Records and Signatures
 - [21 CFR Part 50](#) – Protection of Human Subjects
 - [21 CFR Part 54](#) – Financial Disclosure by Clinical Investigators
 - [21 CFR Part 56](#) – Institutional Review Boards
 - [21 CFR Part 312](#) – Investigational New Drug Application
 - [21 CFR Part 314](#) – Applications for FDA Approval to Market a New Drug
 - [21 CFR Part 600](#) – Biological Products
 - [21 CFR Part 812](#) – Investigational Device Exemptions

- [21 CFR Part 814](#) – Pre-market Approval of Medical Devices

The FDA also publishes a number of Guidances that are useful in the conduct of clinical research. Although the Guidances do not carry the weight of regulations, they represent the current interpretations of the regulations by the FDA. To access these Guidances, go to the FDA homepage at <http://www.fda.gov/>, click on “Guidance Documents” under “Regulatory Information”, then on “Browse Guidance Document Collections by Topic” and then on “Clinical Trials”.

- **Centers for Disease Control (CDC)** <http://www.cdc.gov/>. The CDC has primary responsibility for surveillance and prevention of disease.
- **Centers for Medicare and Medicaid Services (CMS)** <http://www.cms.hhs.gov/>. CMS is the division of HHS that administers the Medicare and Medicaid programs.
- [42 CFR 493](#): Standards and Certification: Laboratory Requirements

The nature of the clinical research being conducted, and the source of the funding if the research is sponsored, determines which federal agency or agencies will be involved.

All clinical research at Columbia or that is conducted by Columbia investigators requiring IRB approval must adhere to the following HHS regulations:

- [45 CFR Part 46](#) – Protection of Human Subjects

In addition, all clinical research at Columbia or that is conducted by Columbia investigators and involves FDA-regulated products (i.e., drugs, devices and biologics) must also adhere to the following FDA regulations, as applicable:

- [21 CFR Parts 50, 56, 312, 600](#) and [812](#)

2. Health Insurance Portability and Accountability Act (HIPAA)

The Health Insurance Portability and Accountability Act of 1996 (**HIPAA**) required the creation of regulations for the protection of health information. These regulations, commonly referred to as the “Privacy Rule”, became effective in 2003 and are codified in Title 45 of CFR, Part 160 and Subparts A and E of Part 164 (the **Privacy Rule**). While the main impact of the Privacy Rule is on uses and disclosure of, and the provision of individual rights regarding, health information, the Rule also affects the use and disclosure of certain health information in connection with research.

The Privacy Rule establishes a category of health information, referred to as **Protected Health Information** or **PHI**, that may be used and disclosed to others only in certain circumstances or under certain conditions.

For a more complete discussion of HIPAA, see **Working with Study Subjects: Informed Consent: Other Consents - HIPAA (Chapter IX, Section G(1))**.

3. Good Clinical Practice (GCP)

GCP is a standard for the design, conduct, performance, monitoring, recording, analysis and reporting of clinical research. GCP is not a single document, but is made up of a combination of FDA regulations and guidance documents, the ICH guidelines for good clinical practice and certain codes of ethical conduct described below. GCP is recognized as the compilation of overall standard operating procedures; at Columbia GCP is considered to describe best practices in conducting clinical research.

ICH Guidelines

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (**ICH**) has published Guidelines for Good Clinical Practice

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Addendum_Step2.pdf. Although it is not yet required by regulation in the United States, the Guidelines have been published in the Federal Register and represent the current thinking of the FDA on good clinical practices. The Guidelines define “Good Clinical Practice” and provide a uniform standard for designing, conducting, recording and reporting on clinical research.

The FDA has published a series of ICH Guidances that can be located by going to the FDA homepage at <http://www.fda.gov/>, click on “Guidance Documents” under “Regulatory Information”, then on “Browse Guidance Document Collections by Topic” and then on “International Conference on Harmonisation (ICH)”. See, in particular, [E6: Good Clinical Practice: Consolidated Guidance](#) (April 1, 1996).

4. Codes of Ethical Conduct

The ethical principles that govern clinical research are codified in the Nuremberg Code, the Declaration of Helsinki and the Belmont Report, which can be found at the following websites:

- [Nuremberg Code](#)

The Nazi atrocities during World War II led to the Nuremberg Code (1949) that includes the principles of informed consent, absence of coercion, scientifically appropriate and well-designed research and beneficence towards human research subjects.

- [Declaration of Helsinki \(21 CFR 312\)](#)

In 1964, the World Medical Association developed the Declaration of Helsinki. This document changed the absolute requirement for informed consent set forth in the Nuremberg Code by allowing consent by legal guardians. The fundamental principle of the Declaration is respect for the individual.

- [Belmont Report](#)

In response to moral outrage with respect to the United States Public Health Service (**Tuskegee**) Syphilis Study, the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research published the Belmont Report (1979) that outlines three fundamental ethical principles for human research: respect for persons, beneficence and justice.

5. University Codes of Conduct

The University has promulgated an Administrative Code of Conduct and a Statement of Ethical Conduct. <http://policylibrary.columbia.edu/administrative-code-conduct-and-statement-ethical-conduct/>. See **Introduction: General University Guidelines (Chapter I, Section H)** in the **Sponsored Projects Handbook**.

F. NewYork-Presbyterian Hospital (NYP)

Many clinical research studies involve subjects who are hospitalized or who use hospital services or data. NYP is Columbia's primary affiliated hospital and is located contiguous to CUMC in Washington Heights. A list of NYP's affiliated hospitals can be found in **Annex C**.

G. Roles and Responsibilities

The following describes the roles and responsibilities of the primary research personnel on a clinical research project and the sponsor. These personnel include the Principal Investigator, any Co-Investigator, the CRC and other research staff. The Departmental Administrator also plays an important role in managing sponsored projects, but is typically not directly involved in conducting clinical research. It is important to remember that, at Columbia, depending on the department or division, it is very possible that responsibilities are shared among the CRC and other administrative or research staff differently than the assignment of responsibilities noted below, and what might be assigned to a CRC here may in fact be the responsibility of another member of the research team, or vice versa.

1. Principal Investigator (PI)

The PI is responsible for the overall conduct and management of the clinical research project, including all administrative, fiscal and scientific matters. Depending on the type of research study, the PI's responsibilities include:

- Assuming overall responsibility for the management of the study;
- Determining protocol feasibility;

- Ensuring that all of the information in the proposal or research protocol is presented in a manner that is complete, accurate and developed according to the practices commonly accepted within the academic community;
- Ensuring that all required approvals are obtained and University forms and certifications are completed in a timely manner;
- Knowing and abiding by the terms and conditions of the award;
- Conducting the work on the project according to the research protocol and investigational plan that was submitted with the original proposal or as subsequently modified by the sponsor in agreement with the PI and the University;
- Ensuring that all work meets the highest ethical standards and is conducted without real or apparent conflicts of interest, in accordance with the University's policies;
- Ensuring that all work performed is conducted in compliance with applicable federal, state and local laws and regulations and with University policies and requirements;
- Ensuring that all research personnel are qualified, have met necessary training requirements, are fully familiar with the research protocol and are kept informed about any modifications of the research protocol;
- Ensuring that the delegation of responsibilities is in accordance with the protocol and any applicable regulations and policies, and that all members of the study team are aware of the delegations;
- Holding regular research team meetings and ensuring communication among all member of the team;
- Determining eligibility of subjects;
- Ensuring that informed consent is properly obtained from study subjects;
- Ensuring appropriate monitoring of subjects;
- Ensuring that all data is obtained, maintained and reported in accordance with the protocol and investigational plan;
- Making medical assessments, evaluating the efficacy of the study medication and determining whether adverse events or unanticipated problems have occurred;
- Submitting reports on the research in a timely manner, according to the sponsor or IRB requirements, including reports of unanticipated problems, adverse events and protocol deviations and violations;
- Managing the project's budget so that funds are spent correctly, taking into account any restrictions imposed by the sponsor and avoiding cost overruns;
- Ensuring that all financial records and reports are accurate and auditable;
- Monitoring the activities of subrecipients, if any;

- Submitting reports on the research in a timely manner and according to the sponsor’s requirements; and
- Completing the formal closeout of the project.

See also **Introduction: Overview of Principal Investigator and Departmental Administrator Roles and Responsibilities (Chapter I, Section G)** in the **Sponsored Projects Handbook**.

See **The ABC’s of FDA Regulated Research: Sponsor-Investigator Research (Chapter II, Section E)** for a description of the responsibilities of a PI who is acting as a Sponsor-Investigator.

See also **Preparing a Sponsored Project Proposal: PI Eligibility (Chapter IV, Section C)** of the **Sponsored Projects Handbook** for a description of eligibility requirements to act as a PI at Columbia.

2. Clinical Research Coordinator (CRC)

The CRC has an integral role in a research study. While the PI is primarily responsible for the overall conduct and management of the clinical research project, the success of many trials is dependent upon the CRC coordinating its activities. Roles classified as CRC roles at Columbia include Study Coordinator, Research Coordinator, Research Nurse, Regulatory Coordinator, Data Manager and Research Assistant. All CRCs should be listed with the role of “Coordinator” in the Personnel section of the Rascal IRB application.

In many departments, CRCs and other research staff share study responsibilities. CRCs often work with DAs, who oversee the financial management of a study. Therefore, it is imperative that the CRC interact closely and frequently with the DA and other staff. Depending on the type of research study, the CRC’s responsibilities include:

- Reviewing the protocol and developing a familiarity with the schedule of events and inclusion and exclusion criteria;
- Assisting in the assessment of study feasibility;
- Working with the PI to develop and implement recruitment;
- Preparing study materials, including informed consent documents, case report forms, enrollment logs and accountability logs;
- Organizing and maintaining study files, including regulatory binders, study specific source documentation and other materials;
- Managing IRB submissions by gathering the necessary documents and obtaining required approvals;
- Managing proposal and contract submissions;
- Attending investigator meetings as required;

- Screening subjects for eligibility as per the protocol inclusion and exclusion criteria;
- Assisting the PI in ensuring appropriate enrollment of study subjects and monitoring recruitment to meet study objectives;
- Coordinating participant tests and procedures;
- Collecting data as required by the protocol;
- Ensuring that all diagnostic and monitoring tests and procedures are reviewed promptly by the PI or his/her designee;
- Monitoring data for completeness and accuracy and responding to protocol data queries from the sponsor, the coordinating center or the contract research organization (**CRO**), as applicable;
- Ensuring that all protocol deviations and violations are appropriately documented and reported to the IRB, the sponsor, the coordinating center and the CRO, as applicable;
- Maintaining effective and ongoing communication with the PI, sponsor and research participants during the course of the study;
- Overseeing study supplies and equipment and maintaining inventory as necessary;
- Obtaining financial account information to facilitate research billing;
- Assisting the PI in reporting information to the IRB, the sponsor, the coordinating center and the CRO, as applicable;
- Retaining all study records in accordance with sponsor requirements and University policies and procedures;
- Facilitating sponsor, IRB and FDA audits; and
- Collaborating with the PI and the University to respond to any audit findings and implement approved recommendations.

The CRC's responsibilities are not, of course, limited to those outlined above; rather, they are dictated by the specific requirements of a particular study.

3. Departmental Administrator (DA)

The DA is responsible for the administrative aspects of a study and is a key individual in the management of the non-clinical, and particularly financial, aspects of the project. While the University places the primary responsibility for the conduct of a sponsored project in all of its aspects on the PI, the PI is assisted in many ways by the DA. Depending on the type of research study, the DA's responsibilities include:

- Working with SPA or the CTO to make sure that budgets and awards are created accurately in the University's financial systems in accordance with the approved award;

- Providing the PI with a copy of the notice of award or contract and discussing with the PI any special award or contractual requirements;
- Understanding the sponsor's restrictions on costs and discussing them with the PI;
- Processing charges to the study based on guidance from the PI;
- Monitoring the award or contract on a regular basis, including monthly reconciliation of accounts;
- Confirming that charges to awards or contracts are appropriate and accurate in adherence to University policies and in compliance with applicable laws and regulations;
- Monitoring subrecipient expenditures and work;
- Assisting with the preparation of financial status reports;
- Monitoring effort reporting; and
- Planning the administrative and financial closeout of the project.

See **Introduction: Overview of Principal Investigator and Departmental Administrator Roles and Responsibilities (Chapter I, Section G)** in the **Sponsored Projects Handbook** for further information.

4. Sponsor

The sponsor is the individual, corporation, institution or government agency that takes responsibility for the initiation, administration and/or funding of an investigation.

Depending on the type of research study, the sponsor's responsibilities include:

- Designing the research study;
- Defining and allocating responsibilities of sites;
- Providing financing for the study;
- Selecting and training qualified PIs;
- Ensuring that the study is conducted in accordance with the investigational plan, governmental regulations and GCP standards;
- Ensuring protocol compliance by sites;
- Monitoring study data for integrity and subject safety;
- Notifying regulatory authorities and sites of adverse events and unanticipated problems;
- Overseeing manufacturing, packaging, labeling, handling and disposition of investigational products; and
- Ensuring retention of study data in accordance with federal regulations.

For FDA-regulated research, the sponsor is the person who initiates a clinical investigation. There are additional responsibilities of a sponsor of a FDA-regulated trial, particularly with respect to the filing of investigational new drug applications and investigational device exemption applications. For FDA-regulated non-industry sponsored clinical research, the PI often acts as both the sponsor and the investigator. See **The ABC's of FDA Regulated Research (Chapter II)** for a brief guide to the regulations relating to FDA research.

The sponsor's team may include a clinical research associate who assists in monitoring study sites. Sponsors often outsource trial management to a CRO.

II. THE ABC'S OF FDA REGULATED RESEARCH

A. Introduction

The FDA is responsible for protecting the health of U.S. citizens by assuring the safety, efficacy and security of drugs, biological products and medical devices, among other things. It regulates clinical studies under Sections 505(i) (drugs and biologics) and 520(g) (devices) of the Federal Food, Drug and Cosmetic Act (**FD&C Act**).

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/FDCAActChapterVDrugsandDevices/default.htm>. Whenever a sponsor intends to administer a new drug or device to a patient, an investigational new drug application (**IND**) or an investigational device exemption (**IDE**) application must be filed with the FDA, unless otherwise exempted. The FDA regulations governing clinical research are extensive and complex. Although sponsors are usually the primary interface with the FDA, it is important that CRCs understand the drug development process, in order to participate knowledgeably in the process, particularly in the situation where the investigator is also acting as the sponsor of a study, as is the case for all clinical studies involving an investigational product for which there is not an external sponsor.

The FDA has three centers that are involved in the regulation of drugs, biologics and devices:

- The Center for Drug Evaluation and Research (**CDER**) is responsible for the safety of chemically synthesized drugs.
- The Center for Biologics Evaluation and Research (**CBER**) has responsibility for vaccines, blood and tissue products and cellular or gene therapies. Biologics are derived from living sources (animals or microorganisms).
- The Center for Devices and Radiological Health (**CDRH**) oversees products such as IV catheters, pacemakers, implantable pumps and synthetic grafts.

The FDA has separate regulations for drugs ([21 CFR 312](#)), biologics ([21 CFR 600](#)) and devices ([21 CFR 812](#)). This chapter will focus on drugs and devices. In addition, this chapter will review the additional compliance issues that relate to sponsor-investigator studies (i.e., studies where the investigator acts as both investigator and sponsor) when a CRC's duties will be more extensive.

See Annex B: Glossary of Defined Terms for definitions of **Drug** and **Device**.

See also the Guidance on investigator responsibilities issued by the FDA entitled [Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects](#) (October 2009).

B. Phases of Clinical Research

The following description of the phases of clinical research relate to drugs, as the FDA has specifically nominated phases in the IND regulations (see [21 CFR 312.21](#)). Similar concepts apply to clinical research with biological products and new devices.

1. Pre-Clinical Research

Before any clinical research involving a potentially viable compound can begin, it must be determined to be reasonably safe for initial testing on humans. During the pre-clinical research phase, the focus is on collecting data and information to establish that humans will not be exposed to unreasonable risks in early phase clinical studies. During pre-clinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through *in vitro* and *in vivo* laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body.

2. Clinical Research

The following describes the various phases of clinical research. Some trials involve more than one phase and are called “bridging trials”.

- **Phase 0** is also known as an exploratory IND study. It is a category of study conducted early in Phase I that involves very limited human exposure and has no therapeutic or diagnostic intent. Phase 0 trials are conducted prior to the typical dose-escalation, safety and tolerance studies (classic Phase I trials) that ordinarily initiate clinical testing. Phase 0 trials can be conducted in patients or normal volunteers, but the duration of dosing must be limited. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078933.pdf>
- **Phase 1** includes the initial introduction of an investigational new drug into humans. The primary concern of Phase 1 is subject safety. These studies are usually conducted in healthy volunteer subjects and are designed to determine the metabolic and pharmacological actions of the drug in humans and the side effects associated with increasing doses. Phase 1 studies also evaluate drug metabolism, structure-activity relationships and the mechanism of action in humans. The total number of subjects included in Phase 1 studies is generally in the range of 20-80 people and such studies are closely monitored by medical personnel. ([21 CFR 312.21\(a\)](#))
- **Phase 2** includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the target disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies usually involve several hundred people and are often double-blind studies. The focus of Phase 2 trials is primarily efficacy. ([21 CFR 312.21\(b\)](#))

- **Phase 3** studies are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies compare the intervention to other standard or experimental interventions and monitor the occurrence, if any, of adverse effects, so as to provide an adequate basis for extrapolating the results to the general population and transmitting that information in the product package. Phase 3 studies usually include several hundred to several thousand people in multi-center studies. ([21 CFR 312.21\(c\)](#))
- **Phase 4** studies are post-marketing investigations intended to monitor the effectiveness of the approved intervention in the general population and to gather additional information about the drug’s risks, benefits and optimal use. The new drug is often tested against an already marketed drug or for other indications. (<http://clinicaltrials.gov/ct2/info/glossary>)

C. Investigational New Drugs

Once sufficient pre-clinical work with a compound has been completed, a sponsor wants to test its diagnostic and therapeutic potential in humans. The FD&C Act requires that all drugs have an approved New Drug Application (NDA) before they can be shipped in interstate commerce. An IND is a submission to the FDA requesting permission to initiate a clinical study of a new drug product. The IND provides the FDA with data necessary to decide whether the new drug and the proposed clinical study pose an unreasonable risk to the human subjects participating in the study.

An IND is required to conduct a human research study if all of the following conditions exist:

- The research involves a “drug” (as defined in Section 201(g)(1) of the FD&C Act ([21 USC 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 [21 CFR 312](#).

The definition of **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”.

[21 CFR 312.3\(b\)](#) defines **clinical investigation** as an experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.

For the purpose 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.

The regulations exempt from the IND requirements clinical studies that meet all of the following exemption criteria:

- The drug product is lawfully marketed in the United States;
- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling 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;
- The investigation is conducted in accordance with the requirements for IRB review and informed consent; and
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

See [21 CFR 312.2](#) and FDA [Guidance for Investigators, Sponsors, and IRBs: Investigational New Drug Applications \(INDs\) - Determining Whether Human Research Studies Can Be Conducted Without an IND.](#)

See **Sponsor-Investigator Research – Summary of IND Process (Section E(3))** below for further information on INDs.

D. Investigational Devices

An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a premarket approval from the FDA.

The IDE regulations ([21 CFR 812](#)) describe three types of device studies: exempt, those with a significant risk device and those with a nonsignificant risk device.

Studies involving a device are **exempt** if they meet one of the following criteria:

- It is a diagnostic device (in limited situations);
- It is 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 study is not to determine safety or efficacy and does not put subjects at risk;

- It is a device used for veterinary or animal research purposes; or
- It is a custom device, unless the device is being used to determine safety or effectiveness ([21 CFR 812.2 \(c\)](#)).

A **Significant Risk Device (SR Device)** is any investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject;
- Is purported or represented to be of use supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety or welfare of a subject ([21 CFR 812.3\(m\)](#)).

A **Nonsignificant Risk Device (NSR Device)** is any device other than an exempt device or a SR Device.

Sponsors are responsible for making the initial risk level determination, but the IRB must review the study and reach its own conclusion. The FDA is the final arbiter of risk level ([21 CFR 812.2\(b\)\(1\)](#)).

The major difference between SR Device and NSR Device studies are in the IDE approval process and in the sponsor's record keeping and reporting requirements, as outlined below:

SR Device Studies

- SR Device studies must follow all of the IDE regulations at 21 CFR 812.
- SR Device studies must have an IDE application approved by the FDA before they may proceed.

NSR Device Studies

- NSR Device studies must follow the abbreviated requirements at 21 CFR 812.2(b), which address labeling, IRB approval, informed consent, monitoring, records, reports and prohibition against promotion. There is no need to make progress or final reports to the FDA.
- NSR Device studies do not have to have an IDE application approved by the FDA.
- Sponsors and IRBs do not have to report IRB approval of a NSR Device study to the FDA.

- A NSR Device study may start as soon as the IRB reviews and approves the study and without prior approval by the FDA.

The IDE regulations prohibit an investigator from providing a non-approved 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 investigator to closely monitor the shipping, storage, use and final disposal of the devices used in the investigation. 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\(a\)](#).

For additional information on devices, including examples of SR Devices and NSR Devices, see FDA Information Sheet Guidances for IRBs, Clinical Investigators and Sponsors: [Significant Risk and Nonsignificant Risk Medical Device Studies](#) (January 2006) and [Frequently Asked Questions About Medical Devices](#) (January 2006).

See **Sponsor-Investigator Research – Summary of IDE Process (Section E(4))** below for further information on IDEs.

E. Sponsor-Investigator Research

The FDA defines a Sponsor-Investigator (**S-I**) as “an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject” ([21 CFR 50.3 \(f\)](#)). Most importantly, this definition goes on to state that: “The requirements applicable to a sponsor-investigator...include both those applicable to an investigator or sponsor.” Thus, for a CRC assisting a PI who is a S-I on a study, it is important to understand these additional requirements, as there will be no corporate or institutional sponsor to fulfill the sponsor's obligations.

A Columbia faculty member may hold an IND or IDE without acting as the PI on a particular study. In such cases, under FDA regulations, that faculty member is the “sponsor” of the study and remains responsible for monitoring the study. For purposes of this Handbook, such faculty member is considered to be a S-I.

1. IND/IDE Assistance Program

In recognition of the additional burdens on a research team, Columbia has instituted an IND/IDE Assistance Program (**IAP**) to assist investigators who act as S-Is and who conduct clinical research studies that require the submission of an IND or IDE application.

The CTO provides advice to investigators generally on FDA regulations, appropriate trial procedures, FDA documentation and trial monitoring.

The IAP has the following components:

- All protocols involving an investigational drug or device that are not industry sponsored must be reviewed by the Manager of Regulatory Science (**Regulatory Science Manager**) of the CTO.
- All S-Is are required to complete an online training course on FDA regulations and responsibilities. See **Getting Started: Training: Mandatory Training – FDA S-I Training (Chapter III, Section C(5))**.
- All CRCs who are involved in greater than minimal risk research are required to complete an online CRC training course on clinical research. See **Getting Started: Training: Mandatory Training – Clinical Research Training (Chapter III, Section C(4))**.
- The Regulatory Science Manager is available to assist S-Is in making a preliminary determination as to whether an IND or IDE is required for a particular study; however, the final determination is made by the IRB.
- For new INDs or IDEs, S-Is are required to have an in-person consultation with the Regulatory Science Manager. In addition, the application itself and the study's monitoring plan are reviewed and approved by the Regulatory Science Manager prior to submission to the FDA.
- All annual reports to the FDA by S-Is are reviewed and approved by the Regulatory Science Manager prior to submission to the FDA.
- Subjects may not be enrolled in a S-I study until both the IRB and the CTO have given their approvals.
- Rascal will generate email reminders for ongoing FDA filing requirements.
- Any faculty member holding an IND or IDE must obtain the approval of his/her department Chair. The IND/IDE holder must send a "Form of Notice by CU faculty IND/IDE Holder" (the **Form of Notice**) to his/her Chair, which must be acknowledged by the PI (if different from the IND/IDE holder), approved by the Chair and submitted to the IRB.
- The applicable department Chair must provide the CTO with the Form of Notice to attest to his/her knowledge of the S-I study and confirm that the department has the necessary resources to support the S-I in the conduct of the study.

More specifically, the services that will be included in the IAP are as follows:

- Explanation of IND/IDE regulations
- Assistance in understanding the obligations of a S-I
- Assistance in determining product classification (i.e., drug, device, biologic)
- Assistance in determining applicability of regulations relating to an IND or IDE
- Assistance in determining contents of an IND or IDE application

- Assistance in preparing and submitting an IND or IDE application
- Assistance in preparing a trial protocol
- Assistance in preparing a S-I monitoring plan for the trial
- Explanation to the clinical study staff of the obligations of a S-I
- Reminder notes of periodic reporting obligations
- Assistance in preparing reports to the FDA
- Assistance in preparing for and responding to FDA inspections.

Columbia faculty and CRCs at the New York State Psychiatric Institute (**NYSPI**) are able to take advantage of the IAP and NYSPI S-Is are subject to the mandatory training and consultation provisions of the Program.

2. Clinical Trials Monitoring Assistance Program

The CTO has also established a Clinical Trials Monitoring Assistance Program (**CTMAP**) to assist S-Is in meeting FDA requirements with respect to monitoring of S-I studies. Monitoring is part of a clinical trial and is the responsibility of the S-I. It is unlikely that there will be an outside monitor for a S-I study. Therefore, the CRC should understand a S-I's monitoring obligations as the CRC will be responsible for many of them.

The CTMAP includes the following components:

- Guidance and instruction for the S-I in the initial design and development of a monitoring plan and strategies for the implementation of the plan. S-Is are encouraged to consult with the CTMAP in the early stages of development of a trial. **The CTO will not monitor the study for the S-I.**
- In connection with the IAP review of IND and IDE annual reports to the FDA, mandatory review of evidence that an appropriate monitoring plan is being implemented and documented.
- Routine and random assessments of the S-I's adherence to the monitoring plan of the trial (including review of significant findings/facts, deviations and deficiencies, conclusions and actions taken or to be taken) and if necessary, recommendation of actions to secure compliance.
- Education for the S-Is and research teams on proper clinical monitoring procedures and reporting.

Columbia faculty and CRCs at NYSPI are able to take advantage of the CTMAP.

3. Summary of IND Process

The following summarizes the process and documentation relating to an IND:

Determining if an IND is needed

To determine whether an IND is needed for a particular study, the following questions should be asked:

- Will human subjects receive a drug that has not been approved by the FDA?
- Will human subjects receive a FDA approved drug for a non-approved indication?

If the answer to either question is “yes”, an IND is most likely needed.

Compiling an IND

The FDA has a specific format that an IND must follow that is described in detail in [21 CFR 312.23](#). The documents include:

- Form FDA 1571: Investigational New Drug Application

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf>

- Form FDA 1572: Statement of Investigator

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

- Form FDA 3454: Certification as to No Conflict of Interest
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048304.pdf>
- Form FDA 3674: Certification of Compliance
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf>
- Cover letter
- Study protocol
- Investigator information (e.g., C.V.)
- Case Report Form (optional)

See also [How Drugs are Developed and Approved](#) for FDA information for S-Is submitting INDs.

IND Approval Process

Once filed, an IND may not go into effect until 30 days after the FDA receives the IND.

The FDA will acknowledge in writing the date it receives the IND. During that 30-day period, the FDA may:

- Request additional information and place a clinical hold on the study. The study may not begin until all concerns raised by the FDA have been satisfied;
- Notify the sponsor that the study is exempt and does not need to have an IND; or
- Approve the study ([21 CFR 312.40](#)).

If the FDA has not placed a clinical hold on the study within the 30-day period, the exemption is deemed to have been approved and the study may begin enrolling subjects once IRB and other approvals have been obtained and all required documentation finalized.

IND Post Approval

After approval of the IND, the S-I assumes all of the responsibilities of both the sponsor and the investigator for maintaining compliance with FDA regulations, FDA guidelines and GCP, as well as the study protocol and any SOPs relating to the study.

Please note that it is very important that all aspects of the study be documented fully and properly to provide evidence of compliance with applicable regulations and the study protocol. Maintaining the Regulatory Binder and patient files correctly is the best way of evidencing such compliance. See *Initiating a Study: Preparation for Initiation – Study Documentation (Chapter VII, Section F(2))*.

The following are the principal responsibilities of a S-I, some of which will be fulfilled by the PI, but many of which may be carried out by the CRC:

- Ensuring that any investigator working on the trial has adequate qualifications;
- Ensuring that facilities remain adequate throughout the study;
- Ensuring that storage, dispensing, instructions for use and disposition of the investigational product comply with regulatory requirements and University policies;
- Ensuring that the IRB approved protocol are followed;
- Ensuring that written consent is obtained from all subjects or their legally authorized representatives, as appropriate, unless waived in accordance with 21 CFR 50.24 (emergency research);
- Ensuring that HIPAA authorization is obtained from eligible subjects, unless waived in accordance with the HIPAA Rules;
- Ensuring that the research staff is adequately informed about the study, that responsibilities have not been delegated to unauthorized individuals and that all activities have been delegated only to persons listed on, and in accordance with, the Delegation of Authority Log (see ***Initiating a Study: Preparation for Initiation – Study Documentation (Chapter VII, Section F(2))*** for a description of a Delegation of Authority Log);
- Ensuring that only eligible subjects are enrolled;
- Ensuring that trial records are accurate, complete and current;
- Ensuring that case report form entries, source documents and other records conform to each other;
- Ensuring that the appropriate corrections of case report forms are made, dated, explained and initialed;
- Ensuring proper monitoring of the study;
- Ensuring that all adverse events (**AEs**) and serious adverse events (**SAEs**) are reported appropriately to the FDA;

- Ensuring that all unanticipated problems involving risks to subjects or others, protocol deviations and protocol violations are reported to the IRB;
- Ensuring that all essential documents are maintained;
- Ensuring that all protocol amendments are submitted to the IRB and all protocol amendments that significantly affect the safety of subjects and/or the scope or scientific quality of the study are submitted to the FDA;
- Ensuring that annual reports are submitted to the FDA; and
- Permitting inspection of the study records by the FDA and assisting in preparation for and conduct any audit.

4. Summary of IDE Process

The following summarizes the process and documentation relating to an IDE:

Determining if an IDE is needed

To determine whether an IDE is needed for a particular study, the following questions should be asked:

- Will human subjects receive a non-FDA approved SR Device?
- Will human subjects receive an approved device for an unapproved use?

If the answer to either question is “yes”, an IDE is most likely needed.

Compiling an IDE

The FDA has a specific format that an IDE application must follow ([21 CFR 812.20](#)). The necessary documents include:

- Cover letter
- Investigator information
- Study protocol
- Monitoring plan.

The FDA requires an electronic copy (**eCopy**) for medical device submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD or other electronic media and accompanied by a signed cover letter and the complete original paper submission. More information about the FDA’s eCopy program, including the new technical standards for an eCopy, can be found in the FDA Guidance: [eCopy for Medical Device Submissions](#).

IDE Approval Process

The approval process for an IDE varies, depending on whether the device is a SR Device or a NSR Device.

- **SR Devices:** After an IDE application is filed with the FDA, the FDA will respond with an acknowledgement letter containing the date that it received the application and an IDE number. A clinical investigation may not begin until 30 days after receipt by the FDA of the IDE, unless earlier notification by the FDA is received, stating that the study may begin. The FDA can disapprove an IDE.
- **NSR Devices:** A NSR Device study requires only IRB approval prior to initiation of a clinical study and an IDE application need not be filed with the FDA. The IRB determines whether or not the device poses a significant risk. If the IRB does conclude that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days and an IDE application must be filed.

IDE Post Approval

After approval of an IDE, the CRC has the responsibilities described in **Investigational Devices (Section D)** above, as well as the responsibilities described in **Sponsor-Investigator Research – Summary of IND Process (Section E(3))** above with respect to an IND trial. As devices are not maintained by the Research Pharmacy at Columbia, it is the S-I's responsibility to prepare and maintain product records, including the following:

- Records of shipment of the device, including name and address of consignee, type and quantity of the device, date of shipment and batch number or code.
- Records of receipt, use or disposition of the device, including type and quantity, date, batch number or code, name of person who received, used or disposed of each device and why and how many units of the device were returned to the manufacturer or otherwise disposed of.
- Any additional records required by the study protocol.

Please note that it is very important that all aspects of the study be documented fully and properly to provide evidence of compliance with applicable regulations and the study protocol. Maintaining the Regulatory Binder and patient files correctly is the best way of evidencing such compliance. See Initiating a Study: Preparation for Initiation – Study Documentation (Chapter VII, Section F(2)).

5. Humanitarian Use Devices

The FDA may grant a Humanitarian Device Exemption (**HDE**) for the use of Humanitarian Use Devices (**HUD**) for studies intended to benefit subjects in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States per year ([21 CFR 814.3 \(n\)](#)). IRB review of HUDs is required. If the IRB determines that the HUD will be used in accordance with the HDE, the use is not considered research and informed consent is not required. If the HUD will be used other than in accordance with the HDE, informed consent is required. In addition, if the HUD is a SR Device, an IDE may be required.

A HUD may be used without prior IRB approval in an emergency situation when waiting for approval would result in serious harm or death to the patient. However, written notification of the emergency use of the HUD should be provided to the IRB within five days of such use.

6. Compassionate Use

Compassionate use is the term used for a means of providing experimental therapeutics prior to final FDA approval for use in humans. This procedure is used with very ill individuals who have no other treatment options.

Compassionate use of an investigational drug, biologic or device falls into one of the following treatment mechanisms and is allowed only after prior review and approval by the IRB, and in most circumstances prior approval by the FDA as well. Prior IRB approval is needed even if only one patient is to be treated under the following mechanisms:

Expanded Access: Treatment INDs or Individual Patient Access to Investigational Drugs/Devices for Serious Diseases: These mechanisms are primarily intended to give seriously ill patients access to experimental drugs or devices where no comparable or satisfactory alternative treatment is available. Although the test article sponsor is expected to continue conventional clinical trials and pursue marketing approvals with due diligence, expanded access studies involve systematic use of experimental treatments and with very rare exceptions require the same review and approval as other research, including both IRB approval and an IDE or IND.

The FDA has developed a new [Form FDA 3926](#) for single patient INDs. This Form can be used by physicians when submitting requests for individual patient expanded access to investigational drugs, including in emergencies. It can also be used for certain submissions to the FDA after an IND is filed. For additional information and the instructions see the [FDA Guidance, Individual Patient Expanded Access Applications: Form FDA 3926](#).

Open Protocol (Parallel Track, Open Label Protocol, Open Label IND) or Continued Access IDEs: Open protocol studies are typically used when controlled trials have ended and treatment is continued so the subjects may receive the benefits of the test article pending marketing approval from the FDA. Prior IRB approval is required.

7. Emergency Use

FDA regulations permit the use of an investigational drug or device, without IRB approval, in very limited circumstances involving an emergency. See **Working with Study Subjects: Exceptions – Emergency Waiver – Individual Emergency (Chapter IX, Section E(3))**. More details about Emergency Use can be found in the IRB SOPs: <http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>.

III. GETTING STARTED: TRAINING

A. Introduction

Prior to participating in any clinical research project, the University requires all personnel involved in such research to take certain training courses in order to ensure that each person has a certain base knowledge of the regulations and policies governing clinical research. Certain training courses are mandatory; other training resources are available, but are not mandatory.

B. Research Compliance Training Finder

The [Research Compliance Training Finder](http://www.columbia.edu/cu/compliance/pdfs/Training_Chart.pdf) is an interactive tool that identifies which research compliance trainings an individual may be required to take. Using a series of research-related questions, the Finder creates a personalized training chart of required and recommended trainings, complete with links to the trainings and the responsible offices. In addition, an overview of training requirements broken down by research roles can be found at http://www.columbia.edu/cu/compliance/pdfs/Training_Chart.pdf.

C. Mandatory Training

1. Human Subjects Protection (HSP)

All research personnel who are engaged in human subjects research, including CRCs, must complete *TC0087: Human Subjects Protection* training as described in **Training: Mandatory Training – Human Subjects (Chapter III, Section C(1))** in the **Sponsored Projects Handbook**. Refresher training must be completed every three years.

If the research involves children, research personnel must complete the Biomedical Research with Minors module within the Human Subjects Protection Training. In addition, if the research is FDA-regulated, research personnel must complete the module on FDA-regulated research.

See also FAQs at http://www.columbia.edu/cu/compliance/pdfs/HSP_FAQs.pdf.

2. GCP Training for NIH-Funded Clinical Trials

The NIH has issued a new policy that requires all NIH-funded investigators and staff who are involved in the conduct, oversight or management of clinical trials to be trained in GCP. The policy takes effect on January 1, 2017. The policy further provides that GCP training should be refreshed at least every three years in order to remain current with regulations, standards and guidelines. Recipients of GCP training are expected to retain documentation of their training.

The Rascal course *TC3450: Good Clinical Practice (GCP) Training* will satisfy the NIH requirements. See **Additional Training Resources: Optional GCP Training (Section D(2))** below. GCP training does not replace HSP training.

The NIH Policy can be viewed at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-148.html>.

3. Financial Conflicts of Interest and Research for the PHS Researcher

Investigators who are funded by the U.S. Public Health Service (**PHS**) or who plan to apply for such funding must complete on-line training in Financial Conflicts of Interest and Research. (Other research sponsors also may require that this training be completed. Contact your SPA or CTO Project Officer for an updated list.) The course is available in Rascal (*TC 1450: Financial Conflicts of Interest and Research for PHS Researchers*) at <https://www.rascal.columbia.edu/>. The training must be renewed every four years.

4. Privacy and Security Training (HIPAA)

All CUMC faculty, staff and students are required to complete general HIPAA training annually. This training includes: (a) HIPAA Privacy and (b) Security Essentials at CUMC. To access these modules, go to <http://securitytraining.columbia.edu> and log in with your UNI and password. Failure to complete the training modules will result in a loss of access to system resources such as Rascal, CROWN, AXIUM and the Columbia Libraries.

In addition, all CUMC research personnel must complete an online course, entitled *TC0019: HIPAA: Health Insurance Portability and Accountability Act Research Training Course*, that is administered through Rascal at <https://www.rascal.columbia.edu/login/tc0019>. Each member of the research team listed on an IRB protocol must complete this training in order for the IRB to permit such person to be involved in the study.

5. Clinical Research Training

All personnel identified as CRCs who are involved in greater than minimal risk research must complete the mandatory CRC Training Program prior to undertaking any research activities. The objective of the Program is to review the major roles and responsibilities of a CRC with a focus on the specifics of conducting research at Columbia, as well as the federal regulations and University policies governing clinical research. Taking the online course *TC0098: Clinical Research Coordinator Mandatory Training*, which consists of six video podcast presentations followed by a multiple choice quiz requiring a score of 80% or better, fulfills this requirement. You can access the course at <https://www.rascal.columbia.edu>. Self-study of this Handbook is strongly recommended.

6. Genetic Research Training

All CRCs who are involved in obtaining informed consent from research subjects who will undergo Genetic Testing when the results of such Genetic Testing will be returned to the subjects must complete *TC3700: Research Coordinator Training: Informed Consent in Genetic Research* in Rascal. See **Working with Study Subjects: Informed Consent – Special Situations – Genetic Research (Chapter IX, Section G(2))** for the definition of Genetic Test and other information about Genetic Testing.

7. FDA S-I Training

Any Columbia faculty member who plan to act as a S-I with respect to an IND or IDE study must complete an on-line training module in Rascal (*TC0096: FDA Requirements of Sponsor-Investigator Studies*) at <https://www.rascal.columbia.edu>, followed by a multiple choice quiz requiring a passing score of 80% or better. The course outlines the FDA regulatory requirements of holding an IND or an IDE. It is recommended that any CRC who manages a study conducted under an S-I-held IND or IDE also take the course.

8. Environmental Health and Safety (EH&S)

Bloodborne Pathogens / Infection Control Modules

The following lists the principal training courses required for personnel involved in clinical research who are exposed to hazardous materials. Additional information about the training courses can be found in **Training: Mandatory Training – Environmental Health and Safety (Chapter III, Section C(5))** in the **Sponsored Projects Handbook**.

- Biological Safety/Bloodborne Pathogens/Infection Control
- Shipping Biological (Infectious and Potentially Infectious) Materials and Genetically Modified Microorganisms
- Shipping with Dry Ice, Exempt Specimens and Excepted Quantities of Dangerous Goods

9. Radiation Safety

The New York City Department of Health regulations require radiation safety training for all personnel whose work brings him/her into contact with ionizing radiation or who works in the immediate vicinity of a radiation source and is likely to receive a dose in excess of 10% of the limits specified in the New York City Health Code. Additional information about radiation safety training courses can be found in **Training: Mandatory Training – Radiation Safety (Chapter III, Section C(6))** in the **Sponsored Projects Handbook**.

D. Additional Training Resources

1. Additional Courses

The following lists the principal additional training resources available at Columbia. More information about the training courses can be found in the following sections of the Sponsored Projects Handbook:

- **Research Compliance Foundations Course for Research Administration: Chapter III, Section D(1)**
- **Sponsored Projects Essentials: Chapter III, Section D(1)**
- **Columbia University Certification in Administration of Sponsored Projects: Chapter III, Section D(1)**
- **Financial Conflicts of Interest and Research: Chapter III, Section D(1)**
- **IRB: Chapter III, Section D(2)**

2. Optional GCP Training

Training in GCP, while not required by the University, is recommended for all clinical research personnel. The Rascal course, *TCC3450: Good Clinical Practice (GCP) Training* (the **GCP Course**), may satisfy clinical trial sponsors that require training in GCP. The GCP Course is not a substitute for the HSP training described in **Getting Started: Training: Mandatory Training-Human Subjects Protection (HSP)** above in **Section C(1)**.

The GCP Course is maintained by the Collaborative Institutional Training Initiative (CITI), but must be accessed through Rascal. The course offers researcher three course options:

- **Good Clinical Practice Course, US FDA Focus** – This course is intended for research personnel involved in drug, device or biologic studies who would benefit from FDA-focused training.
- **Good Clinical Practice Course for Clinical Trials Involving Medical Devices (International Focus)** – This course is intended for research personnel involved in device studies.
- **Good Clinical Practice Course for Clinical Trials Involving Investigational Drugs (ICH/International focus)** – This course is intended for research personnel involved in drug and biologic studies who would benefit from a more internationally focused training.

To provide sponsors proof of completion, as well as a list of topics covered, researchers may print a completion report from CITI. For further information about GCP courses, contact RCP.

3. Billing Compliance

The CUMC Office of Billing Compliance (**OBC**) offers online Annual Billing Compliance Training that is tailored for clinical research billing. Every CRC who is involved in the generation or submission of medical claims, as well as in any aspect of revenue management, should take this training course. Research billing compliance training details the complexities of billing for clinical research and highlights Medicare rules for clinical research billing. It can be accessed at the OBC website: <http://www.cumc.columbia.edu/dept/compliance/>

See also **Preparing for a Study: Project Feasibility and Study Documents: Budgets (Chapter IV, Section E)** for a more detailed explanation of clinical billing compliance.

E. Medical Surveillance

Any individual having patient contact must undergo annual medical surveillance exams. For any CRC who is a new hire, this should be scheduled immediately following his/her start date. For all other CRCs, this appointment must be scheduled annually. CUMC departments will schedule CRCs for medical surveillance appointments with Workforce Health & Safety (**WHS**) located in the Harkness Pavilion, 1st Floor South ((212) 305-7580). A CRC should bring the following items to his/her appointment:

- CUMC ID card
- Request form signed by supervisor
- Immunization records, if available
- Purified protein derivative (**PPD**) or chest x-ray results, if completed within prior year.

The medical surveillance examination will be routine and the employee will not be charged for the services. The components of the exam are as follows:

- Medical history
- Physical examination with vital signs
- Two-step PPD administration
- Review of immunity to rubella, measles and varicella
- Tetanus-diphtheria vaccine (offered every 10 years)
- Bloodborne pathogen exposure surveillance
- Hepatitis B virus vaccine series (if applicable) or documented declination
- Surveillance for latex sensitivity

The first visit will consist of drawing blood, planting a PPD and conducting a baseline physical examination, which should take approximately two hours. A second visit, which should take approximately 30 minutes, will be scheduled for PPD assessment within 48-72 hours after the PPD has been planted. A third visit, if necessary, will be scheduled by WHS to plant a second PPD. A clearance form will be issued upon completion of this process.

CRCs are expected to follow up with their scheduled appointments. Because medical surveillance is required by the New York State Public Health Law, employees who have not completed medical surveillance exams may be placed off duty without pay until they are cleared by WHS or terminated. Compliance with medical surveillance and annual health review is a condition of continued employment. See <http://www.ehs.columbia.edu/medsurveill.html>.

IV. PREPARING FOR A STUDY: PROJECT FEASIBILITY AND STUDY DOCUMENTS

A. Introduction

Before any clinical research project is undertaken, there must be an initial review to determine whether the study is appropriate for Columbia and for the particular PI who will lead the project. There are two types of feasibility analyses: one by the PI and his/her research staff and, if the project is sponsored, the other by the sponsor.

Once a study is deemed feasible, unless a sponsor has already approached Columbia to see if there is interest in participating in a study, it must be funded. The University can provide assistance in finding funding. See **Preparing for a Study: Project Feasibility and Study Documents – Finding Funding (Section C)** below.

The principal study documents are the protocol, the budget, the consent form, the case report form (**CRF**) and for a clinical trial, the clinical trial agreement (**CTA**). The protocol is the document that describes the objectives, design, methodology, statistical considerations and plan for the conduct of the study. The consent form is used to describe the study for potential subjects and is used to evidence a subject's consent to participate in the study. The budget sets forth the financial needs of the study. The CRF is the primary reporting tool for the study. The CTA contains important provisions governing the performance of a clinical trial. Although a CRC may not be involved in the drafting of all of these documents, it is critical for him/her to understand the contents in order to manage the conduct of a study.

B. Feasibility Assessment

1. Internal Assessment

Any PI who has (a) been approached by an industry sponsor to join a particular research project, (b) intends to file a grant application with a non-industry sponsor or (c) wants to initiate an internally funded project must assess whether the proposed study is a good fit for Columbia and his/her research team. It is always better to not agree to participate in a study than to agree and be unable to enroll a sufficient number of subjects. The CTO and SPA are available to assist research teams in conducting feasibility studies. The PI, the CRC and other members of the research team should assess the project based on the following criteria:

Scientific Validity

The team must determine whether or not a study has scientific validity. Will the project add to scientific knowledge? Will patients benefit from the study? Are any ethical concerns addressed?

Recruitment Potential

Recruiting subjects for clinical research is key to the success of the study. See **Working with Study Subjects: Recruitment and Enrollment (Chapter VIII)** for a more detailed discussion of recruitment techniques. Initially, the team must determine if, given the potential patient population, the number of subjects to be enrolled and the rate of enrollment is realistic. Is the enrollment period sufficient in duration to achieve recruitment goals? Are there studies vying for the same patient population at Columbia or the community that would impede recruitment? Will potential patients be motivated to participate in onerous or invasive study procedures?

Financial Feasibility

Given the costs associated with conducting a research study and the proposed budget, the team must determine whether the research study in question is financially feasible. Will the study revenue cover applicable costs, such as equipment, procedures, administration, salaries, IRB fees, pharmacy fees and data archiving fees? What is the cost to the site per subject and what is the cost to the site per screen failure? Are screen failures reimbursed by the sponsor? How will enrollment that is lower than anticipated affect study revenue?

Resource Assessment

The team must determine whether the necessary resources to run the study are available. How large will the research team be and what level of clinical sophistication is needed for the staff? What is the number and nature of the CRFs? Are they paper or electronic? If electronic data capture is utilized, is the program user friendly? Do laboratory values need to be transcribed? Are patient diaries/electronic diaries utilized, and if so, do they need to be transcribed/transmitted? Is test article accountability/reconciliation complex? What is the frequency and duration of monitoring visits? Does the constitution of the study team adequately support the trial considering their responsibilities on other active trials?

2. Pre-Study Site Visit

After the PI has been notified of a possible study and a Confidentiality and Disclosure Agreement (see **Preparing for a Study: Review and Finalization of Proposals and Contracts: Review Process – Industry Sponsored Clinical Research (Chapter VI, Section B(2))**) has been signed, an industry sponsor typically evaluates the site in person. The pre-study site visit (also known as a pre-study site evaluation or assessment) is the sponsor's opportunity to discuss the study with the PI and assess the PI's experience, expertise and interest in the study. The sponsor will also evaluate whether the site has

appropriate facilities, staff and equipment and will discuss recruitment potential. The site evaluation is the opportunity for the sponsor to determine whether or not the site meets its criteria for participation in the trial and for the research personnel to ask questions about the protocol and study requirements.

3. Biostatistics Consulting Service

The assistance of a statistician is very important in the development of the experimental design of a study, the analytical methodology and the interpretation of study data. The Biostatistics Consulting Service (BCS) is a clinical research consulting service, supported by the CTO and the Irving Institute for Clinical and Translational Research that provides short term consultations of one or two meetings with limited follow-up free of charge to CUMC faculty. The BCS is staffed by members from the Department of Biostatistics at the Mailman School of Public Health. The BCS staff members have extensive expertise in clinical trials as well as other experimental designs and can provide state-of-the-art guidance on statistical analysis and study design for all stages of research.

You must request the services of the BCS through the Irving Institute website <http://irvinginstitute.columbia.edu/resources/biostatistics.html>. Investigators needing statistical advice or assistance in data analysis are typically accommodated within a few days of their request. However, during high volume periods, it may take up to two weeks to accommodate a request. The consultation process begins with an initial meeting to discuss the project. If the statistical needs of the project can be addressed within approximately five hours, the BCS will provide the statistical support for the project. If based on the meeting it is determined that longer-term support is required, for example, to write a scientific paper or to produce a grant application, the project will be referred to other faculty members in the Department of Biostatistics for co-authorship or salary support (via serving as a co-investigator on the grant proposal).

C. Finding Funding

Columbia has a number of resources available to assist faculty and staff to identify funding for research and training. See **Finding Funding (Chapter II)** in the **Sponsored Projects Handbook** for a full explanation of sources of funding and University resources.

D. Protocols

As a protocol describes the particular study being considered, no two protocols are alike. A protocol for an industry sponsored study is usually prepared by the sponsor. If the study is non-industry sponsored, the information to be included in the protocol is typically described in the sponsor's RFP/RFA or study announcement, as well as on the sponsor's website.

The guidelines for ICH GCP describe the elements necessary for a study protocol. The current guidelines (version E6) can be found at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

A typical protocol contains at least the following information, to the extent that it is relevant:

- **Study Objective:** a statement of the main hypothesis and purpose of the study.
- **Study Design:** a description of the design, methodology and procedures of the study, including endpoints.
- **Study Population:** a description of the subjects to be included in the study and the anticipated number of subjects.
- **Subject Selection and Withdrawal:** a description of the inclusion and exclusion criteria, the recruitment methods and withdrawal of subjects.
- **Study Drugs or Devices:** a description of the drug or device, method for assigning subjects to the treatment group, preparation, administration, dosing and dispensing of the study drug/device and monitoring.
- **Statistical Plan:** a description of the statistical approach and methodology for the study.
- **Safety and Adverse Events:** a description of the procedures for data and safety monitoring for assuring subject safety and reporting adverse events.
- **Data Handling and Record Keeping:** the specifics of data collection and handling, confidentiality and retention of records.

Some federal agencies have templates for generating protocols that include sample language and guidance on required elements:

National Cancer Institute (NCI):

https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm

National Heart, Lung and Blood Institute (HLBI):

<http://www.nhlbi.nih.gov/files/docs/clinical-research-guide-protocol-template.doc>

National Institute of Allergy and Infectious Diseases (NIAID):

<https://www.niaid.nih.gov/media/niaid-protocol-template-guidance>

National Institute of Neurological Disorders and Strokes (NINDS):

http://www.ninds.nih.gov/research/clinical_research/toolkit/protocol.htm

The NIH and FDA are developing templates with instructional and sample text for NIH-funded investigators to use in writing protocols for Phase 2 or 3 clinical trials that require INDs or IDE applications. The agencies' goal is to encourage and facilitate the

preparation of protocols that are consistently organized and contain all of the information necessary for the application to be properly reviewed. The templates are available at <http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials>.

E. Budgets

Once a study protocol is completed, a formal budget must be prepared to specifically analyze which costs will be incurred during the study and which of such costs will be covered by the particular sponsor.

There is an extensive discussion of how to prepare a sponsored project budget in **Preparing a Sponsored Project Budget (Chapter V)** in the **Sponsored Projects Handbook**. That Chapter covers a detailed explanation of direct costs and indirect costs that are permitted to be charged on federal and non-federal projects.

Clinical research, and, in particular, clinical trials, require special budgetary considerations and include such items as:

- Medical evaluations
- Radiology and special studies
- Laboratory fees
- Pharmacy costs
- Special equipment or supplies
- IRB review (for industry sponsored trials only)
- Administration
- Study monitoring visits and sponsor site visits
- Preparation of CRFs
- Patient reimbursement
- Advertising

In addition, for billing purposes, you must be familiar with the categories of costs related to patient care.

Patient Care Costs

When preparing a clinical study budget, the PI and the CRC must distinguish between “standard of care costs” (also known as “usual care costs”) and costs that are solely related to the research project, as the categorization of costs will affect the billing of such costs. Billing for clinical studies may be complex because often more than one entity is responsible for the costs incurred in a trial. Possible payors are the sponsor or the patient and/or his/her insurer (including Medicare). As a general rule, the sponsor pays for services, drugs, devices and treatments that are solely for research purposes and the patient and his/her insurer pays for standard of care treatment.

Standard of Care Costs are items and services (routine and ancillary) ordinarily furnished in the treatment of patients by hospitals or providers of patient care under the supervision of the physician or other responsible health professionals. Such items or services may be diagnostic, therapeutic, rehabilitative, medical, psychiatric or any other related professional health services. These expenses are for care that would have been incurred even if the research study did not exist.

In some rare cases, a sponsor will pay for standard of care costs. For example, reimbursable standard of care costs can be paid when the research hospitalization extends beyond that ordinarily required for usual care, or imposes procedures, tests or services beyond usual care, whether in an inpatient or outpatient setting. The CTO will also seek reimbursement from the sponsor of costs that were initially considered to be standard of care, but are finally determined to be research costs.

Research Patient Care Costs are the costs of routine and ancillary services provided by hospitals and providers of patient care to individuals participating in research programs. The costs of these services normally are assigned to specific research projects through the development and application of research patient care rates. Research patient care costs do not include: (a) the otherwise allowable items of personal expense reimbursement, such as patient travel or subsistence, consulting physician fees or any other direct payments related to all classes of individuals, including inpatients, outpatients, subjects, volunteers and donors, (b) costs of ancillary tests performed in facilities outside of the hospital on a fee-for-service basis (e.g., in an independent, privately owned laboratory) or laboratory tests performed at a medical school/university not associated with a hospital routine or ancillary service, (c) recruitment or retention fees or (d) the cost of data management or statistical analysis of clinical research results.

If the study is being funded by NIH, only “allowable costs” may be charged to the grant. The NIH Grants Policy Statement provides that “if the patient is receiving service or care that neither differs from usual patient care nor results in expenses greater than those that would have been incurred if the study had not existed, the patient is considered to be [treated] for usual care purposes and the grant will not support the costs. When the research extends the period of [treatment] beyond that ordinarily required for usual care, or imposes procedures, tests or services beyond usual care, whether in an inpatient or outpatient setting, the grant may pay the additional costs. The grantee must decide whether, in fact, the hospitalization period, the tests or the services have been extended beyond or added to what would ordinarily have been expected, and to what extent.” See “Research Patient Care Costs” in the NIH Grants Policy Statement (10/10) – Part II: Terms and Conditions of NIH Grant Awards
http://grants.nih.gov/grants/policy/nihgps/HTML5/section_19/19.1_general.htm.

As budgetary and billing issues are complex in clinical studies, it is very important that you work closely with your SPA Project Officer or CTO Budget Analyst from the beginning of budget preparation.

As the budget is being prepared, your SPA Project Officer or CTO Budget Analyst will review the protocol, the grant award or the CTA budget, the informed consent forms and the schedule of events and will work with the PI and CRC to prepare a Budget Worksheet, a sample of which is included in **Annex F**. CRCs should also review the study documents to ensure that costs are allocated correctly and that all research costs will be covered by the sponsor. If the coverage is not clear or additional costs should be covered, your SPA Project Officer or CTO Budget Analyst can provide assistance in contacting the sponsor to negotiate changes in the budget.

Many patient care costs incurred in clinical trials at Columbia are incurred by NYP. Such costs are determined by NYP. For federally sponsored clinical trials, the University is not permitted to pay more than certain prescribed rates for hospital services that are based on agreed upon Medicare reimbursement rates and are discounted from the rate that NYP would charge non-Medicare patients. The research rates are negotiated with the government on an annual basis and are published in a Chargemaster maintained by NYP.

The OBC is available to advise on clinical billing issues, including Medicare rules. See **Financial Management of a Study - Medicare (Chapter XIV, Section D)** for a description of Medicare reimbursement.

If the Research Pharmacy or the Department of Radiology or Anesthesiology will be used in the study, the following cost estimate forms should be completed prior to finalizing the budget:

- Pharmacy Cost Estimate Form
- Radiology Cost Estimate Form
- Anesthesiology Cost Estimate Form

The Forms are available on the CTO website:
https://cto.cumc.columbia.edu/for_investigators.html .

Indirect costs (officially named **Facilities and Administrative (F&A) Costs**) are recovered in government sponsored clinical trials as they are in other federally sponsored projects. See **Preparing a Sponsored Project Budget: Facilities and Administrative (F&A) Costs (Chapter V, Section C)** in the **Sponsored Projects Handbook** for a discussion of F&A Costs. However, F&A rates cannot be paid on any cost relating to research patient care costs. When calculating indirect costs for a grant, prior to applying the F&A rate, the research patient care costs should be removed from the total direct costs.

Your SPA Project Officer or CTO Budget Analyst is always available to assist you in preparing a budget.

F. Case Report Forms (CRFs)

CRFs are documents used to systematically collect data for clinical trials that will be analyzed to establish study outcomes and subject data. CRFs standardize the collection of study data and help to ensure that the medical, statistical, regulatory and data management needs of the study are met. The CRC transcribes data from hospital records, office visit records, lab and x-ray results, etc. to CRFs.

Because the protocol defines the data to be collected and documented, the CRF should be constructed in parallel with the creation of the study protocol. The data collected on CRFs should be those items that are truly necessary to answer the objectives of the study. Data is generally collected on subject visits and CRFs should clearly spell out the process for gathering information.

Typical data that are included in a CRF are:

- Visit schedule
- Inclusion and exclusion criteria
- Medical history
- Demographic information
- List of medications
- Lab data
- Clinical end points and outcomes
- Adverse events/serious adverse events/unanticipated problems.

Sponsors are increasingly using CRFs in electronic format (**eCRFs**), so that data is entered directly into a computerized data base on a website established by the sponsor or into a computer provided by the sponsor. Like CRFs, eCRFs must have corresponding source documentation and it is possible that these documents are maintained in paper format.

An example of a CRF can be found in **Annex F**. Sponsors often provide the research team with their own CRF that must be used during the study.

See **Source Documentation and Case Report Forms: Case Report Forms (CRFs) (Chapter XI, Section C)** for more information on CRFs.

V. PREPARING FOR A STUDY: IRB APPROVAL

A. Introduction

When conducting clinical research, the safety of human subjects is paramount. The safeguards for human subjects are primarily considered by the IRB. The role of the IRB is to protect the rights and welfare of individuals who are participating as subjects in a research study. Once a study is approved, the IRB reviews modifications to the study protocol, conducts continuing reviews at least annually for non-exempt research, audits studies and, if necessary to protect subjects, can suspend or terminate the project.

The HRPO is the administrative office that provides support to the Columbia IRBs. Columbia has seven IRBs: six at CUMC and one on the Morningside campus. One of the six CUMC IRBs reviews all oncology studies that require initial review by a convened IRB, another reviews studies where the primary focus is on genetic or genomic research and the third reviews only protocols initially eligible for expedited review. The HRPO also has an Administrative Review Committee at CUMC comprised of IRB staff. Projects that constitute exempt research, and protocols that do not meet the regulatory definitions to be considered human subjects research, are reviewed by members of this Committee. See **Administrative Review Committee (Section D(4))** below.

The HRPO convenes an IRB Executive Committee that is made up of the Chairs and Vice Chairs of the IRBs, the Executive Director and other managers of the HRPO and the Vice President for Research Operations twice a month to discuss regulations, policies, compliance cases and issues relating to studies in which more than one IRB is involved or a PI is an IRB member.

There is a wealth of information about the IRB, applicable regulations, the review process, etc. on the IRB website: <http://www.cumc.columbia.edu/dept/irb/>

B. IRB Review

Any investigator at Columbia who is planning to engage in human subjects research must submit a protocol and related materials, including the informed consent form, to the IRB, respond to any concerns raised by the IRB and wait for formal approval before enrolling subjects.

In addition to traditional biomedical studies, IRB approval must be obtained when the research involves the following:

- Human subjects to test devices, products or materials that have been developed through research or to evaluate environmental alterations (i.e., habitat modifications)

- Data collected through intervention or interaction with individuals. Intervention includes not only physical procedures (such as drawing blood), but also manipulation of a subject's environment and some observations
- Private information that can be readily identified with individuals, even if the information was not collected specifically for the study in question. Examples include student records and medical records
- Bodily materials such as cells, blood or urine, tissues, organs, hair and nail clippings even if the researcher did not collect these materials. (Depending on the nature of the study, such research may be considered “not human subjects research” or exempt from IRB review if materials are not personally identifiable and if the materials were collected prior to the initiation of the research project. There are exceptions, e.g., for some device studies and studies that involve certain kinds of genetic testing. Consultation with the IRB staff is recommended.)
- Studies conducted to gain generalizable knowledge about categories or classes of subjects such as employees, students and/or patients. This includes a doctoral dissertation or master’s thesis.
- Studies that utilize a Limited Data Set that contains information considered to be identifiers according to HIPAA.
- Studies that utilize de-identified data for which specific data security provisions are required by the applicable data use agreement. The purpose of the IRB review is to confirm that the plans for data storage are appropriate.

If you have any questions about whether a particular activity is research that must be reviewed by the IRB, please contact the HRPO.

The IRB may approve research only after it has determined that the following requirements, as described in [45 CFR 46.111](#) and [21 CFR 56.111](#), if applicable, have been satisfied:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to the anticipated benefits and the importance of the knowledge that may be gained;
- Selection of subjects is reasonable in view of the purpose of the research and the setting in which it will be conducted;
- Legally effective informed consent will be obtained from each prospective subject, or the subject's legally authorized representative, unless waived by the IRB. The informed consent process and the consent form must provide the appropriate information and be understandable to a lay person;
- Informed consent will be appropriately documented by a signature on a consent form unless this requirement is waived by the IRB;

- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- When appropriate, adequate provisions exist to protect the privacy of subjects and to maintain the confidentiality of data; and
- Additional safeguards have been included in the study to protect the rights and welfare of vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged individuals.

If any of these requirements are not met, the IRB will either recommend modifications that will ensure the study satisfies these requirements or disapprove the study.

The review criteria listed above are the minimum that the IRB consider. Requirements of other applicable federal regulations (e.g., HIPAA), state laws (e.g., Confidentiality of Records of Genetic Tests) and institutional policies (e.g., Data Security, Disclosure of Social Security Numbers) must also be satisfied before the IRB can approve a new protocol, renewal or modification.

C. Timing of IRB Review

At Columbia, the IRB and other review processes generally run on parallel tracks. For industry sponsored studies, the IRB protocol is reviewed and other approvals obtained while the CTA is being negotiated and finalized. For non-industry sponsored studies, investigators often wait until they know that their proposal will be funded before submitting a protocol to the IRB, although the NIH and certain other federal agencies, under the “Just in Time” program, request applicants whose applications fall within a certain percentile or priority score range to submit additional information, including evidence of IRB approval, prior to the formal notice of award. See **Review and Submission of a Sponsored Project Proposal: Just in Time/Additional Information Requested (Chapter VI, Section H)** in the **Sponsored Projects Handbook** for additional information about Just in Time.

All oncology studies must be approved by the Herbert Irving Comprehensive Cancer Center Protocol Review and Monitoring Committee after submission of the protocol to the IRB, but prior to IRB approval. See **Preparing for a Study: Review and Finalization of Proposals and Contracts: Approval Process – Additional Approvals and Certifications (Chapter VI, Section D(2))** for information on other approvals that must be obtained prior to IRB approval.

D. Steps in Obtaining IRB Approval at Columbia

1. Creation of Protocol

The IRB review process at Columbia begins with the creation of the study IRB protocol in Rascal. The IRB protocol has a specific format and differs from a sponsor’s protocol.

It contains general information, a list of the personnel working on the study, scientific and lay abstracts of the study, descriptions of specific elements of the study and other pertinent information. The IRB application in Rascal is accessed by selecting “Human Subjects” and “Create a Protocol,” at <https://www.rascal.columbia.edu>. Information may be entered in fields and documents may be attached electronically. There is also a feature that permits construction of informed consent documents called the “Consent Form Builder” that can be accessed by selecting “Human Subjects” and “Consent Forms” at <https://www.rascal.columbia.edu>. Other required documents (e.g., appendices for Hazardous Materials, HIPAA forms and study instruments) can be attached to the protocol in the Rascal file and relevant documents that are available only in paper form can be scanned and attached.

The IRB provides guidance and tools to facilitate protocol submission to the IRB at <http://www.cumc.columbia.edu/dept/irb/>. Tools include: templates for protocols and consent forms, tips for efficient IRB review and reviewer forms. In addition, the HRPO, in collaboration with the Irving Institute for Clinical and Translational Research, has created a liaison service, whereby an IRB staff member provides in person consultations to answer questions about the IRB review process, policies and Rascal.

All actions relating to a specific study, including material submitted, information entered, correspondence generated, internal IRB notes and documents, history and status, are stored together electronically as “events” (per Rascal terminology) within the Rascal “file” for each overall project. IRB staff and members may view all entries and attachments for a given event, once the event has been submitted, and may attach documents to the submission, but may not otherwise modify the submitted material.

2. Submission of Protocol

The protocol must be submitted to the IRB through Rascal. Detailed instructions on how to submit a protocol to the IRB can be found at <http://www.cumc.columbia.edu/dept/irb/submit.html>.

The IRB has an abbreviated submission process for all studies that have a complete external protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering of the study summary into the Rascal fields is not required, as the IRB relies on the stand-alone protocol for review by all of its members.

3. HRPO Pre-Review

Each incoming new study receives a thorough pre-review by HRPO staff utilizing a detailed pre-review form that is available on the HRPO/IRB website under “Policies” and “IRB Review”. <http://www.cumc.columbia.edu/dept/irb/policies/> The pre-review is designed to ensure that each protocol includes the necessary information to proceed with IRB review and that each study will receive all relevant regulatory considerations. Once

a study has completed pre-review, it will be assigned to an IRB or the Administrative Review Committee and either logged in (if complete) or returned to the PI to respond to pre-review comments.

4. Administrative Review Committee

At CUMC, an Administrative Review Committee that is comprised of HRPO staff members reviews protocols that meet exemption criteria or appear to not meet the regulatory definitions of *research* or *human subject*.

Once a protocol is logged in and assigned to the Administrative Review Committee, a Committee member reviews the protocol and determines whether the protocol falls into one of the following categories:

- Not human subjects research
- Exempt research

If the protocol does not meet the criteria for either of the above categories, it will be assigned to an IRB for expedited or full Board review.

Not Human Subjects Research

An IRB Chair or a member of the Administrative Review Committee may determine that the project described in the protocol does not meet the definition of “research” (as defined in the applicable federal regulations), or does not involve “human subjects” (as defined in the applicable federal regulations). See **Annex B** for the definitions of **research** and **human subjects**. If that determination is made, no further IRB review of the project is required.

Exempt Research

A protocol may be determined to be exempt from the requirements of the federal regulations for the protection of human subjects if all procedures fall into one or more of six specific categories of research specified in [45 CFR 46.101\(b\)](#).

The exempt categories are:

- Educational Practices Research
- Educational Testing, Survey or Observational Research
- Educational Testing, Survey or Observational Research involving Public Officials
- Research using Existing Data/Records/Specimens
- Research on Public Benefit Programs
- Taste and Food Quality Research

Even if it would appear that a project falls into one of the exempt categories, the determination as to whether a study is exempt must be made by the IRB. At Columbia,

the decision is made by any member of the HRPO staff on the Administrative Review Committee or a Chair of an IRB.

Any research protocol that is believed to be exempt should be submitted in Rascal providing the same information as in a non-exempt study, except that the study description can be limited to explaining how the research fits in one or more of the exempt categories and a consent form is not required. Although obtaining informed consent is not required for exempt studies, the IRB strongly recommends that for studies involving direct interaction between the investigator and the subjects, participants should minimally be informed of the following:

- the activity is research;
- the procedures that are involved;
- the nature of the risks;
- participation is voluntary; and
- the subject may withdraw from the study at any time.

Expedited Review

A protocol may qualify for expedited review if it involves no more than minimal risk to subjects and includes only procedures described in nine categories of research specified in <http://www.hhs.gov/ohrp/policy/expedited98.html>. Expedited reviews at CUMC are handled by a separate IRB, with the Chairs of the other five IRBs designated as the reviewers. Expedited reviews on the Morningside campus are processed by the Chair, Vice Chair or an experienced member of the Morningside IRB.

5. Full Board Review

Full Board review is required for all human subjects research protocols that are not eligible for exemption or expedited review. The protocol is reviewed by a member of the IRB who has been designated as the reviewer by the Chair of the IRB to which the protocol has been assigned and is presented and discussed at a convened meeting of the Board, at which a quorum must be present. Recommendation for action must be voted upon, and a majority must approve the recommendation.

6. Post Review Status

Following an expedited or full Board review, a protocol falls into one of the following status categories:

Approved: This means that the study is approved and may proceed if all other required approvals have been received. Any limitations, restrictions and/or conditions imposed by the IRB are stated in the approval letter. **Note:** *this status category is used for both expedited and full Board reviews.*

Pending: This means that the PI must modify the protocol and/or the consent form in a way that is specified by the IRB. Once the specified changes have been made within Rascal, the PI resubmits the protocol in Rascal and the changes are reviewed by the Chair or a designated reviewer. Once the reviewer confirms that the changes required by the Board have been made, the protocol status will be changed to “Approved.” This is permissible because the Board has sufficient information to make the required determinations that all IRB review criteria had been met when the requested changes were made. **Note:** *this status category is used for full Board reviews only.*

Returned: This means that there are more changes needed in the protocol and/or consent form than could be completely specified by the Board or IRB reviewer, i.e., the Board or reviewer did not have sufficient information to make the required determinations that all IRB review criteria had been met without reviewing the protocol again. The PI must address the issues that were raised by the reviewer or Board and resubmit the protocol in Rascal. The protocol will be reviewed again by the reviewer or at another Board meeting. **Note:** *this status category is used for both expedited and full Board reviews.*

Denied: This status is rare. The PI should discuss denial with the Board Chair to determine what can be done to change the protocol in such a way that it can be approved by the IRB. **Note:** *this status category is used for full Board reviews only.*

In the event that a protocol that is on an agenda for review at an IRB meeting cannot be reviewed, e.g., the quorum is lost or the primary reviewer cannot present the study, the status of the protocol will be “deferred”. The protocol will remain in the IRB queue and be added to an upcoming meeting agenda.

If a PI has not responded to IRB comments on his/her protocol within 60 days (for protocols eligible for expedited review) or 90 days (for protocols that required full Board review), the protocol must be withdrawn by the PI and the PI must re-submit the protocol under a new IRB number.

7. IRB Meeting Schedules

Each of the IRBs generally meets twice per month. At CUMC, at least one IRB meets every week, except in certain holiday weeks. Meeting schedules for both the CUMC and Morningside IRBs are posted on the applicable IRB website at <http://www.cumc.columbia.edu/dept/irb/about.html> or <http://www.columbia.edu/cu/irb/about.html>.

8. Approval

Final IRB approval (i.e., approval to enroll subjects or collect identifiable private information about subjects) may not be given until evidence of the following has been entered into Rascal:

- PI approval
- Herbert Irving Comprehensive Cancer Center Protocol Review and Monitoring Committee approval, if applicable
- FCOI Committee approval and/or administrative clearance, if applicable
- Joint Radiation Safety Committee or Radioactive Drug Research Committee approval, if applicable
- Institutional Biosafety Office approval, if applicable
- Completion of all relevant training courses by the PI (mandatory training of other research personnel may be completed after IRB approval, but prior to involvement of such personnel in the study).

See **Getting Started: Training: Mandatory Training (Chapter III, Section C)** and **Preparing for a Study: Review and Finalization of Proposals and Contracts: Approval Process (Chapter VI, Section D)** for a more detailed discussion of the foregoing requirements.

IRB approval letters are issued electronically and are available on the Print Menu page in Rascal for the applicable study. Once approved, the study status will appear in a number of places in Rascal. Statuses appear on the Protocol Overview Page and the History Page for a given protocol, as well as the Rascal Data Sheet and the Study Description.

9. Protocol Modifications

Any proposed change to the protocol, the protocol procedures (including subject selection and the consent process), consent forms, personnel, documents (including recruitment ads, investigator brochure and/or study instruments) must be submitted to the IRB for review and approval prior to implementation unless such a change is necessary to eliminate or minimize an imminent harm to subjects. Any other changes that may affect a participant's willingness to participate in the study must also be submitted for prospective IRB review.

All protocol modifications should be submitted to the IRB by creating a modification event in Rascal. A summary of all of the substantive changes being proposed should be included in the text box "Summary and Explanation of Proposed Changes." Detailed information about the changes may be included in a separate document that is attached to the modification. It is also necessary to indicate whether the modification requires changes to the consent form.

If the protocol was eligible for expedited review, and the proposed change(s) are not such that the protocol would no longer be eligible for expedited review, then the modification may also be reviewed under the expedited review process.

If the overall protocol requires review by a convened IRB, and the change is non-substantive in nature, the IRB may approve such a change by expedited review. Full Board review of the modification is required if the proposed changes are substantive in

nature (e.g., increase in risk, addition of a treatment arm, expansion of the study population to include vulnerable subjects).

If it is discovered that there is an imminent harm to subjects, the investigator should implement any change necessary to reduce or remove such harm and subsequently submit a modification to the IRB so that such change is approved by the IRB for all subsequent research activities under the protocol. Changes made without prospective IRB approval, to address an imminent harm to subjects, are considered exceptional situations that are neither deviations nor violations.

Protocol deviations (i.e., changes that are not in accordance with the approved protocol, but are approved in advance by the IRB, such as exceptions to inclusion and exclusion criteria that have been authorized by the sponsor) and violations (i.e., changes that are not in accordance with the approved protocol and have occurred prior to or without IRB approval) that occur during the study should also be submitted as modifications, unless the change constitutes an unanticipated problem involving risks to subjects; the latter should be submitted using the unanticipated problem reporting module. See **Unanticipated Problem, Adverse Event and Protocol Deviation/Violation Reporting (Chapter XIII)**.

When a modification includes new information relating to risks, additional or modified procedures, or other factors that may affect subjects' willingness to continue participation, the IRB must consider options for providing this information to participants. Such options may include obtaining signatures on a revised consent form, adding an addendum to the consent form, providing an information sheet to subjects or verbally informing subjects by telephone, in person or by email. Regardless of the method selected, content of the documents or scripts that will be used should be provided to the IRB for review, with the means of documenting notification specified.

10. Continuing Review

All non-exempt human subjects research for which there are plans to continue beyond the expiration of the current IRB approval must be re-reviewed and approved by the IRB for an additional period. Based on information submitted by the PI, the IRB will evaluate, to the extent possible via administrative review, whether all regulatory and institutional criteria have been met during the conduct of the research to date. The focus of the continuing review is to provide oversight and evaluate whether the IRB review criteria continue to be met, e.g., if the risk/benefit ratio is still considered to be acceptable, and to assess the conduct of research activities to date.

Federal regulations ([45 CFR 46.109\(e\)](#)) provide that the IRB should conduct a continuing review not less than once a year and more often if the degree of risk warrants it. Ordinarily, an IRB protocol expires one year from the date of the prior approval or, in the case of a protocol that had a full Board review, from the date of the most recent convened meeting at which the protocol was reviewed by the Board. When any of the following

(non-inclusive) situations exist, the Board will consider an approval period of less than one year:

- the need for increased monitoring to evaluate anticipated risks;
- scant safety data due to early introduction of a test article in clinical studies (e.g., early Phase 1 studies); or
- the need for increased monitoring to evaluate potential noncompliance or for projects conducted by investigators who have previously failed to satisfy IRB requirements.

Exempt protocols must be renewed every five years. The purpose of this renewal is to confirm that the study is ongoing and continues to meet the exempt criteria.

Notification that renewal is required is sent automatically by Rascal to investigators at 90, 60 and 30 days prior to the expiration date of the current IRB approval. Investigators are required to submit renewal requests in Rascal and are encouraged to submit appropriate reports for ongoing research activities 60 days prior to the expiration date of the IRB approval for the study.

If approval of the renewal is not obtained prior to the expiration date of the protocol, all study-related procedures and funding, if applicable, must be halted. No new subjects may be enrolled and any study-related intervention or data analysis must cease unless not continuing the study would seriously and adversely affect the safety or well-being of already enrolled subjects. If this is true, the PI should submit a request to the IRB for continuation of enrolled subjects as soon as possible, together with a letter of explanation.

To renew a study, investigators must complete the “Renewal Information Form” and the “Subjects” section in the Rascal IRB module. In addition, investigators must attach the following documents, as applicable: a summary of unanticipated problems; recent Data Safety Monitoring Board reports; copies of the current informed consent documents, and any newly proposed revisions to the consent documents; documentation to support study changes; any withdrawal of subjects from the research or complaints about the research since the last IRB review; and any other relevant information, especially information about changes in risks associated with the research. For federally funded multiple year projects, a copy of the most recent Progress Report should be included. For all sponsored projects, if changes in the terms or type of funding have occurred, the “Funding” section should be updated and the appropriate documentation attached. All information in the renewal submission that is automatically populated (carried over) by Rascal should be reviewed and confirmed for accuracy, with updates where necessary.

Each Board has the authority to determine, at its discretion during the continuing review process, which research activities need verification, from sources other than the investigator, that no material changes in the research have occurred since the previous IRB review. To determine which projects need verification, the Board will consider such things as an unexplained and sudden increase in risk to subjects, FDA audits, site visits conducted by authorized personnel, reports from “whistleblowers,” etc. Verification may

be obtained through contact with the sponsor, FDA or cooperative group, as applicable, by audit of the investigator's files, and via requests for information from a coordinating center or monitoring board.

When initial review was conducted by an expedited review procedure, continuing review will usually be conducted via an expedited process, provided that all study procedures continue to fall within one or more of the federal categories of expedited review and continue to present no more than minimal risk to subjects.

Modifications to approved research may be considered by the IRB during continuing review and must be approved prior to implementation. When a modification is submitted in conjunction with a renewal request, the IRB may approve both or approve the renewal without the modification.

11. Study Closure

Requests by researchers for closure of an approved project are reviewed by a primary reviewer prior to ratification at a convened meeting. The IRB reviewer will have access to the staff reviewer's notes, and will evaluate information provided about the number of subjects enrolled, unanticipated problems and study results to determine whether closure is appropriate and to ensure that all outstanding issues have been adequately addressed.

If follow-up of participants for safety reasons is permitted or required by the IRB, participants should be so informed, and any unanticipated problems or adverse outcomes should be reported to the IRB. In these cases, IRB approval should remain current.

See **Study Closure (Chapter XV)** for a further discussion of a study closure.

12. For Cause Study Suspension or Termination

Under the IRB Policy, [Noncompliance with Human Subjects Regulations](#), each Board has the authority to suspend or terminate the approval of research that is not being conducted in accordance with federal and state laws and regulations and University policies governing the protection of human subjects in research, or is not being conducted in accordance with stipulations previously imposed on the research activity by the IRB. The Policy spells out the procedural requirements that must be met prior to suspension or termination.

However, any Chair of an IRB or the Executive Director of the HRPO may unilaterally suspend a study if he/she receives information that requires the immediate action for the protection of human subjects or to address a concern regarding potential noncompliance with federal or state regulations or University policies; such actions should occur when, in the judgment of the Chair or the Executive Director of the HRPO, it would be inappropriate to wait until the next meeting of the IRB or, for cases in which more than one IRB is involved or a PI is an IRB member, the Executive Committee of the IRB.

Any suspension or for cause termination of IRB approval will be reported promptly to OHRP and the FDA, if required.

13. External IRB Review

New York State Psychiatric Institute (NYSPI)

Studies originating in the Department of Psychiatry and utilizing NYSPI patients, data or facilities may be reviewed by the NYSPI IRB in accordance with the agreement between NYSPI and Columbia; all other Department of Psychiatry studies are reviewed by the Columbia IRB.

Weill-Cornell Medical College

Studies for which there will be research activity at both CUMC and the Weill-Cornell Medical College (**Cornell**) campus may be eligible for review by only one of the IRBs (i.e., either CUMC or Cornell) under the CUMC-Cornell IRB Authorization Agreement (**IAA**). This agreement is applicable when the PI has an appointment at both institutions or when there is collaboration between faculty with appointments at each institution. Depending upon whether the Cornell or CUMC IRB will be the IRB of record (to be decided by the IRB chairs and/or directors), the submission process at CUMC will vary. If CUMC will rely on the Cornell review, the Cornell application, approval letter and consent form must be attached in Rascal, and the protocol will be reviewed by the CUMC IRB Chair for local issues only. If Cornell will rely on the CUMC IRB review, the submission to CUMC will be the same as for a protocol that will be conducted solely at CUMC, with the addition of an explanation of bi-campus activity and plans to submit to the Cornell IRB, for review of local issues, under the IAA.

If CUMC and Cornell constitute separate study sites in a multicenter study that includes additional sites, the CUMC IRB should be used for the CUMC study activities and the Cornell IRB for Cornell study activities.

14. Central IRBs

An increasing number of studies are using one IRB, i.e., the IRB of one institution participating in the study or an independent IRB, as the IRB of record for all institutions involved in the study (a **Central IRB**). Central IRBs have been used in cancer and other consortia for a number of years and Columbia has long-standing relationships with several Central IRBs, such as the NCI Central IRBs and the Fred Hutchinson Cancer Research Center IRB. Going forward, the HRPO will consider permitting reliance on a Central IRB on a case by case basis if it believes that the Central IRB meets the University's standards and can reasonably be expected to provide increased efficiencies.

The Columbia IRBs have themselves been designated as Central IRBs for several protocols and consortia. Columbia investigators who wish to learn about reliance on a Central IRB or single IRB or having Columbia serve as a Central IRB or the single IRB should consult with the HRPO. Each use of a Central or single IRB has its own set of operating procedures and the investigators and the HRPO work together to ensure that all of the responsibilities of the Central IRB Reliance Agreement have been met.

On June 21, 2016, the NIH issued a final Policy on the Use of a Single Institutional Review Board of Record for Multi-Site Research, effective May 25, 2017. This Policy documents the NIH's expectation that all sites participating in multi-site studies involving non-exempt human subjects research funded by the NIH will use a single IRB to conduct the IRB review for all of the sites.

VI. PREPARING FOR A STUDY: REVIEW AND FINALIZATION OF PROPOSALS AND CONTRACTS

A. Introduction

Any sponsored project proposal or contract must be reviewed by the appropriate University administrative office to ensure that all of the sponsor's requirements have been met, the proposal complies with all governmental laws and regulations and University policies and the University's legal interests are protected and its risks minimized. In addition, the budget must be thoroughly reviewed for accuracy, allowability and completeness.

The processes and documentation for reviewing and submitting a proposal to a government or foundation sponsor are very different from those steps taken in an industry sponsored clinical trial. This Handbook will describe both.

The University has two offices that assist investigators in preparing project proposals and that are authorized to review and submit proposals or negotiate contracts relating to clinical research: SPA and the CTO. The CTO negotiates contracts for all industry sponsored clinical trials and clinical research. SPA has responsibility for all other proposals (except those referred to in the following paragraph). If you are not certain as to which office is responsible for your study, please call SPA or the CTO for assistance. See also **Introduction: Clinical Research – Definitions of Clinical Research and Clinical Trials** (Chapter I, Section D(1)).

CTV has responsibility for the negotiation of agreements for certain industry sponsored non-clinical research and will not be discussed in this Handbook. See **Introduction: Other University Offices Involved in Sponsored Research – Columbia Technology Ventures (CTV)** (Chapter I, Section F(1)) and **Preparing a Sponsored Project Proposal: University Offices That Can Assist with Proposal Development and Submission and Other Agreements - CTV** (Chapter IV, Section E(3)) in the **Sponsored Projects Handbook** for information on CTV.

Please note that all sponsored research proposals and contracts must be signed on behalf of the University by certain officers designated by the Trustees; with respect to clinical research, these officers are designated personnel either in SPA or the CTO.

For descriptions of SPA and the CTO and which proposals are reviewed by each, see **Introduction: Primary University Offices Involved in Sponsored Research: Office of the Executive Vice President for Research (EVPR) – Office of Research**

Administration (ORA) (Chapter I, Section E(1)) in the Sponsored Projects Handbook.

B. Review Process

1. Non-Industry Sponsored Clinical Research

A flow chart in **Annex E** outlines the review and approval process for a NIH clinical study, which is representative of many non-industry sponsored clinical research projects.

Rascal Proposal Tracking

A CRC may initiate the review process by entering the research proposal into the Rascal proposal tracking module (**Rascal PT**). To enter a proposal:

- Go to the Rascal website at www.rascal.columbia.edu.
- Select “Grants and Contracts”
- Log in with your UNI and password
- Select “Create a Proposal”
- Complete, at a minimum, the following fields:
 - Primary responsible department number
 - Submitting to (which campus office)
 - Deadline date
 - Deadline type
 - Title
 - Abbreviated title
 - Answers to questions about involvement of Select Agents, Hazardous Materials, Recombinant DNA and Human Gene Transfer
 - PI’s name (on Personnel page)
 - Agency/Sponsor name (on Sponsor page)
- Obtain Rascal “Proposal Tracking ID Number”

Receipt of a Rascal Proposal Tracking ID Number means that the proposal has been registered in Rascal.

Proposal and Budget Review

At least five business days prior to the sponsor’s submission deadline, the following documents should be submitted to the applicable Project Officer in SPA assigned to the PI’s department in final form:

- Grant application, proposal or contract.

- Budget and Budget Justification. See **Preparing For a Study: Project Feasibility and Study Documents: Budgets (Chapter IV, Section E)** for a discussion of budgets.
- FCOI disclosure forms. Up-to-date FCOI disclosure forms must be completed in Rascal for all individuals who will conduct the proposed research, including the PI and each other person identified in the proposal. For more information on FCOIs, see **Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications – Financial Conflicts of Interest (FCOIs) (Chapter VI, Section E(1))** in the **Sponsored Projects Handbook**.
- Finalized **Rascal PT Record** that includes:
 - All of the fields required to register a proposal in Rascal (see **Rascal PT** above)
 - Subdepartment number (if none, use default of 000000)
 - Agency/Sponsor address
 - Line 1 Budget
 - Begin and end date of budget
 - Building and space information (building, floor, room)
 - Evidence that all approvals and certifications required prior to submission have been obtained.
- Subawards. If the proposal includes subawards, a statement of work, budget, budget justification and face sheet signed by each subrecipient’s institutional official. For more information on subawards, see **Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications - Subawards (Chapter VI, Section E(10))** in the **Sponsored Projects Handbook**.

The applicable Project Officer in SPA will work with the research team to finalize the grant application, proposal or contract and the other documentation prior to the sponsor’s submission deadline.

2. Industry Sponsored Clinical Research

A flow chart in **Annex E** outlines the review and approval process for a typical industry sponsored clinical study that is described in more detail below.

Confidentiality and Disclosure Agreement (CDA)

The review process typically begins with receipt of a CDA. The CDA is a contract that defines the terms and criteria used to assure that a sponsor and the University will maintain the confidentiality of study-related information, including data, methods and procedures, and will not use this information for any purpose other than that described in the CDA. Typically, a sponsor will not provide the study protocol to the PI prior to the execution of the CDA.

CDA Review

If a sponsor contacts a PI to elicit whether he/she has an interest in participating in a study, the PI should request that the CDA be sent to his/her designated Project Officer in the CTO. If the PI receives the CDA directly, it should be forwarded to that individual. In order to review the CDA, the CTO requires receipt of the following documents and information:

- PI name and contact information
- Sponsor name and contact information
- CRO name and contact information, if applicable
- Electronic copies of the CDA and any CDA-related correspondence from the sponsor.

The designated reviewer will review and, if necessary, negotiate the CDA, although negotiation of a CDA is unusual. The review process is ordinarily completed in 3-5 days. After the terms have been agreed upon, the CDA is executed. **Please note that the CDA may only be signed on behalf of the University by an approved signatory in the CTO.** If the PI is required to sign the CDA, it will be sent to him/her for signature following execution by the CTO signatory. If the PI is not required to sign, he/she will be notified when the CDA is fully executed. <http://cto.cumc.columbia.edu>

Budget Review

The CTO Budget Analyst assigned to the PI's department will develop and negotiate the study budget with the sponsor. However, the PI and CRC should always review the budget with the CTO Budget Analyst to ensure that all appropriate study related and departmental or divisional costs are included.

See **Preparing for a Study: Project Feasibility and Study Documents: Budgets (Chapter IV, Section E)** for a discussion of budgets.

Clinical Trials Agreement (CTA) Review

Once the CDA has been executed and a draft budget is being reviewed, the CTO Project Officer assigned to the PI's department will negotiate the CTA with the sponsor and assemble the necessary documents required to prepare a file and process a project. The CTA is a contract between Columbia and the sponsor that defines the scope of work and budget and includes provisions relating to costs, payment terms, proprietary rights, indemnification and publication rights.

The CTO has negotiated Master Agreements with a number of pharmaceutical companies and is endeavoring to sign additional Master Agreements. Master Agreements cover all of the general terms of a CTA, including indemnification, publication rights and intellectual property, and only the specific payment terms relating to a study are included

in a Supplement to the Master Agreement, thereby virtually eliminating negotiation time and permitting faster approval of the CTA.

Tax Exemption Certificate

The CTO requires submission of a Tax Exemption Certificate with any industry sponsored projects.

C. Other Agreements

The CTO and SPA also negotiate Data Use Agreements (**DUAs**) and Material Transfer Agreements.

1. Data Use Agreements (DUAs)

A DUA is a contract used for the transfer of data that has been developed by the University or another academic institution, the government or private industry, where the data is nonpublic or is otherwise subject to some restrictions on its use. Universities want to ensure that DUA terms protect confidentiality when necessary, but permit appropriate publication and sharing of research results in accordance with University policies and applicable laws and regulations.

DUAs at the University are initially reviewed by the HRPO to ascertain whether the data is identifiable and thus in need of greater confidentiality protections and whether the DUA is consistent with the study protocol. They are then reviewed by the CTO or SPA to negotiate other contract terms.

DUAs include those relating to limited data sets under HIPAA. See **Working with Study Subjects: Other Consents – HIPAA (Chapter IX, Section G(1))** for further information on such DUAs.

A DUA also allows investigators to impose appropriate limitations on users. Such an agreement usually indicates the criteria for data access and whether or not there are any conditions for research use, and can incorporate privacy and confidentiality standards to ensure data security at the recipient site and prohibit manipulation of data for the purposes of identifying subjects. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm pertaining to NIH grants.

2. Material Transfer Agreements (MTAs)

A MTA is a contract used for the acquisition of various biological and research materials and occasionally data, developed by the University or another academic institution, the government or private industry. The MTA defines the rights of the provider and the

recipient with respect to the material and any derivatives. The University has the same set of concerns as are applicable to DUAs and such issues – publication rights, use of research results, ownership of technology, confidentiality, etc.

MTAs are initially reviewed by the HRPO to establish whether the MTA involves human subjects research. They are then reviewed by the CTO or SPA to negotiate other contract terms.

D. Approval Process

Prior to finalization of any non-industry sponsored grant application or proposal or any industry contract, the following approvals need to be obtained:

1. PI Certification and Departmental and School Approvals

See **Review and Submission of a Sponsored Project Proposal: PI Certification and Departmental and School Approvals: Departmental and School Approvals (Chapter VI, Section D(2))** in the **Sponsored Projects Handbook** for a description of University requirements relating to PI departmental and school approvals of any research project.

2. Additional Approvals and Certifications

In addition to the PI and departmental and school approvals referred to above, certain other approvals must be obtained or certifications made prior to commencing any clinical research project. These steps are described in detail in **Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications (Chapter VI, Section E)** in the **Sponsored Projects Handbook**. The **Special Approval Summary Chart (Chapter VI, Section E(13))** in the **Sponsored Projects Handbook** also contains a table that provides links to websites where more detailed information can be obtained.

Please note that an IRB approval letter for any clinical research study will not be issued until all of the following approvals and training certifications described in Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications (Chapter VI, Section E) in the Sponsored Projects Handbook (see links to Chapter VI, Section E below) are in hand:

- **Financial Conflicts of Interest (Section E(1))**
- **Human Subjects (Section E(3))**
- **Environmental Health and Safety (Section E(5))**
- **Radiation Safety (Section E(6))**

In addition, the following approvals are needed, if applicable:

- **Human Embryos and Embryonic Stem Cells (Section E(7))**
- **International Research (Section E(8))**
- **NewYork-Presbyterian Hospital (Section E(9))**

The following approvals are mentioned briefly in **Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications (Chapter VI, Section E)** in the **Sponsored Projects Handbook**, but because they play a more important role in clinical research, are described in more detail below.

Radiation Safety

Investigators who wish to enroll subjects in research that results in the exposure to or absorption of ionizing radiation are required to obtain written approvals from the Joint Radiation Safety Committee (**JRSC**) of CUMC, NYP and NYSPI or, in certain cases, the University's Radioactive Drug Research Committee (**RDRC**).

The JRSC is authorized by the NYC Department of Health to evaluate and approve proposals for, and maintain surveillance over, all use of radioactive materials and radiation generating devices at CUMC, NYP and NYSPI, as well as to evaluate and oversee any administration of radioactive materials, whether for research or clinical treatment. JRSC approval is required for any research with human subjects that includes procedures involving any ionizing radiation beyond that received in standard clinical practice. Sources of ionized radiation include x rays, mammography, DEXA scans, dental x-rays, fluoroscopy, nuclear medicine, PET scans, CT scans, etc.

The FDA requires investigators to submit an IND for radioactive drugs, biologics and "cold" kits to be used for radiolabelling and radionuclide generators for investigational purposes, including testing their safety and efficacy. The FDA permits the RDRC to review and approve certain basic science research involving the administration of unapproved radiopharmaceuticals intended to solely obtain information about human physiology, patho-physiology, biochemistry or drug metabolism, in lieu of obtaining FDA approval of an IND. RDRC requirements include dose limits (radiological and pharmaceutical); qualifications of investigators; proper licensure for handling radioactive material; selection and consent of research subjects; the quality of the radioactive drugs used; research protocol design; and reporting of adverse reactions.

IRB approval may not be granted without evidence of JRSC or RDRC approval. Therefore, the JRSC or RDRC application process should begin no later than the filing of the protocol with the IRB in order to have timely review. The CRC should contact the Radiation Safety Program personnel for additional information regarding the application and review process. To access the JRSC and RDRC Applications and the Guidelines that accompany each, go to <http://www.ehs.columbia.edu/RadiationFormsMC.html>.

The Research Radiation Safety Handbook (<http://evpr.columbia.edu/content/selected-resources>) contains additional detailed information on the JRSC and RDRC application process.

Human Gene Transfer of Recombinant DNA Molecules

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (<http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines>) (the **rDNA Guidelines**) provide the regulatory framework for any research, regardless of the source of funding, involving recombinant or synthetic nucleic acid molecules. The University's Institutional Biosafety Committee (**IBC**) is charged with overseeing compliance with the rDNA Guidelines. For further information, please see the University's Recombinant DNA Policy: Requirements for Submission, Approval and Use (<http://ehs.columbia.edu/RecombinantDNA.pdf>).

The rDNA Guidelines apply generally to research with recombinant and synthetic nucleic acids and in particular to **human gene transfer**, which is the deliberate transfer into human research participants of either (1) recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules or (2) synthetic nucleic acid molecules, or DNA or RNA derived therefrom that meet certain criteria (collectively, **Recombinant DNA Molecules or rDNA**).

All clinical research involving human gene transfer requires prior submission to the NIH's Office of Biotechnology Activities (**OBA**). Such research is reviewed by the IBC, concurrently with IRB review. Investigators must submit with the protocol an [Application for the Use of Recombinant DNA Molecules in Human Gene Transfer](#) which is available online or by request from biosafety@columbia.edu. In order for the IRB to track submissions, Rascal Appendix A (Recombinant DNA) is also required. Note that this submission process will change in 2017 when the Application will become an Appendix in Rascal and Appendix A will no longer be required.

The following additional information is required by the IBC at the time of submission of the Application:

- If the Sponsor will be responsible for reporting to the OBA, a copy of the letter sent to the OBA informing them of this delegation.
- The scientific abstract. The abstract from the grant proposal may be used.
- A copy of the Clinical Investigator's Brochure.
- The informed consent document that is currently (or will be) under consideration by the IRB.
- A copy of the Sponsor's letter to the OBA describing the object and rationale for the research. The requirements are detailed in Appendix M of the Guidelines.
- A copy of the NIH's response (Outcome of Initial Review by the Recombinant DNA Activities Committee (the **RAC Response**)) to the Sponsor's Appendix M.

- If the RAC Response includes comments by members of the Recombinant DNA Activities Committee (the **RAC**), the Sponsor's reply to the comments.

Effective April 27, 2016, the NIH instituted a streamlined review process for human gene transfer protocols subject to the rDNA Guidelines. The IBC will now determine whether the protocol would significantly benefit from review by the RAC. Factors to consider include whether:

- The protocol uses a new vector, genetic material or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.
- The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.
- The proposed vector, gene construct or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies involved to evaluate the protocol rigorously.

If RAC review is warranted, the PI and the IRB will be provided with a written assessment from the IBC. Requests for RAC review must originate from the oversight body (i.e., the IRB or IBC) involved in the initial site review (not necessarily the University). The PI will be responsible for ensuring that the oversight body submits the request to the NIH (as well as the documentation outlined in Appendix M – I – A of the rDNA Guidelines). The IBC may not approve a protocol until the RAC has completed its review.

A PI must report serious adverse events that are unexpected and possibly associated with human gene transfer intervention to the IBC (by notifying EH&S) and the OBA as soon as possible, but in any event within 15 calendar days of the PI notification of the sponsor or within 7 calendar days if life-threatening or fatal. In addition, the PI must submit to SPA annually certain information about protocols described in the rDNA Guidelines.

Infectious Agents and Bloodborne Pathogens

Investigators must attach a Rascal Appendix B (Infectious Agents) to protocols for clinical research involving the administration of infectious agents to or the collection of infectious agents from, research subjects.

In lieu of submitting a Rascal Appendix C (Human Materials or Other Potentially Infectious Materials), PIs who work with such materials must complete an IRB Human Materials Attestation in Rascal to confirm that all research staff have undergone appropriate training, engineering controls and medical surveillance are in place, personal protective equipment is available and regulated medical waste will be handled appropriately.

Additional Approvals

The following additional approvals not referred to in the **Sponsored Projects Handbook** are required to the extent that they are relevant to the particular research project:

Herbert Irving Comprehensive Cancer Center (HICCC)

The HICCC Protocol Review and Monitoring Committee (**PRMC**) serves as the scientific review committee for research protocols that are related to the prevention, detection or treatment of cancer. PRMC review and approval is required prior to review by the IRB for non-industry sponsored trials and occurs concurrently with the IRB review of industry sponsored trials. The PRMC conducts an initial review of all cancer research protocols, a review of all protocol modifications and an annual re-review of the research. See <http://hiccc.columbia.edu>

The submission will be routed to the PRMC in Rascal if the researcher indicates in his/her submission to the IRB that the research involves an intervention designed to diagnose, treat, prevent or provide supportive care to subjects with or at risk of developing a form of cancer, including the use of specimens, observation or surveillance, the examination of outcomes or the evaluation of care. For non-industry sponsored trials, the protocol will remain in the IRB queue during the PRMC review and IRB pre-review will occur concurrently. Once the PRMC issues its approval, the protocol can be assigned to an IRB member for review. In all cases PRMC review is required before final IRB approval is issued.

Irving Institute for Clinical and Translational Research

Columbia has been the recipient of a NIH Clinical and Translational Science Award (**CTSA**) since 2006 that provides most of the funding for the Irving Institute for Clinical and Translational Research (the **Irving Institute**). The Irving Institute provides resources intended to support and develop translational research at CUMC, inpatient and outpatient facilities, core laboratories, nutritionists, bioinformatic experts and statistical consultants. Its inpatient unit, the Clinical Research Resource, provides services such as initiating and maintaining intravenous infusions, obtaining EKGs, drawing blood, running studies that require frequent or pharmacokinetic specimen acquisition, and processing specimens. Any research that is intended to use the Clinical Research Resource must be approved by the Irving Institute. An application form can be completed online at <http://irvinginstitute.columbia.edu/pdf/CRCApplication.pdf>.

National Governmental Services (NGS) or Centers of Medicare and Medicaid Services (CMS) Determination

Federal regulations require that in order to be eligible for Medicare reimbursement, all clinical trials using certain types of investigational devices must receive approval in advance by NGS, Columbia's local Medicare contractor, or by CMS. It is a University policy that Category A or Category B device trials for which charges will be billed to Medicare may not commence enrollment of subjects without such approval.

IDE Studies Approved by the FDA prior to January 1, 2015

Investigational device studies under an FDA-issued IDE that begin with the letter “G” and post-market approval studies or registries of carotid stents (**Covered Studies**) that were approved by the FDA prior to January 1, 2015 must be submitted to NGS for a coverage decision prior to enrollment of subjects into the study. Submission to NGS cannot occur until the protocol has received IRB approval and the contract for the study has been executed.

IDE Studies Approved on or after January 1, 2015

Covered Studies that are approved by the FDA on or after January 1, 2015 must be submitted to CMS for a coverage decision prior to enrolling subjects in the study. In order to have a Covered Entity approved for coverage, a member of the research team should contact the sponsor and request that the sponsor submit the required documentation to CMS. CMS will post the names of the Covered Studies that have been approved for coverage on the CMS website on a weekly basis. In addition, “NYPH/CUMC” must be listed as a research facility on the ClinicalTrials.gov record for the study. If “CUMC” or “Columbia University” is listed as a research facility, the sponsor should be contacted to change the name of the research facility to “NYPH/CUMC”.

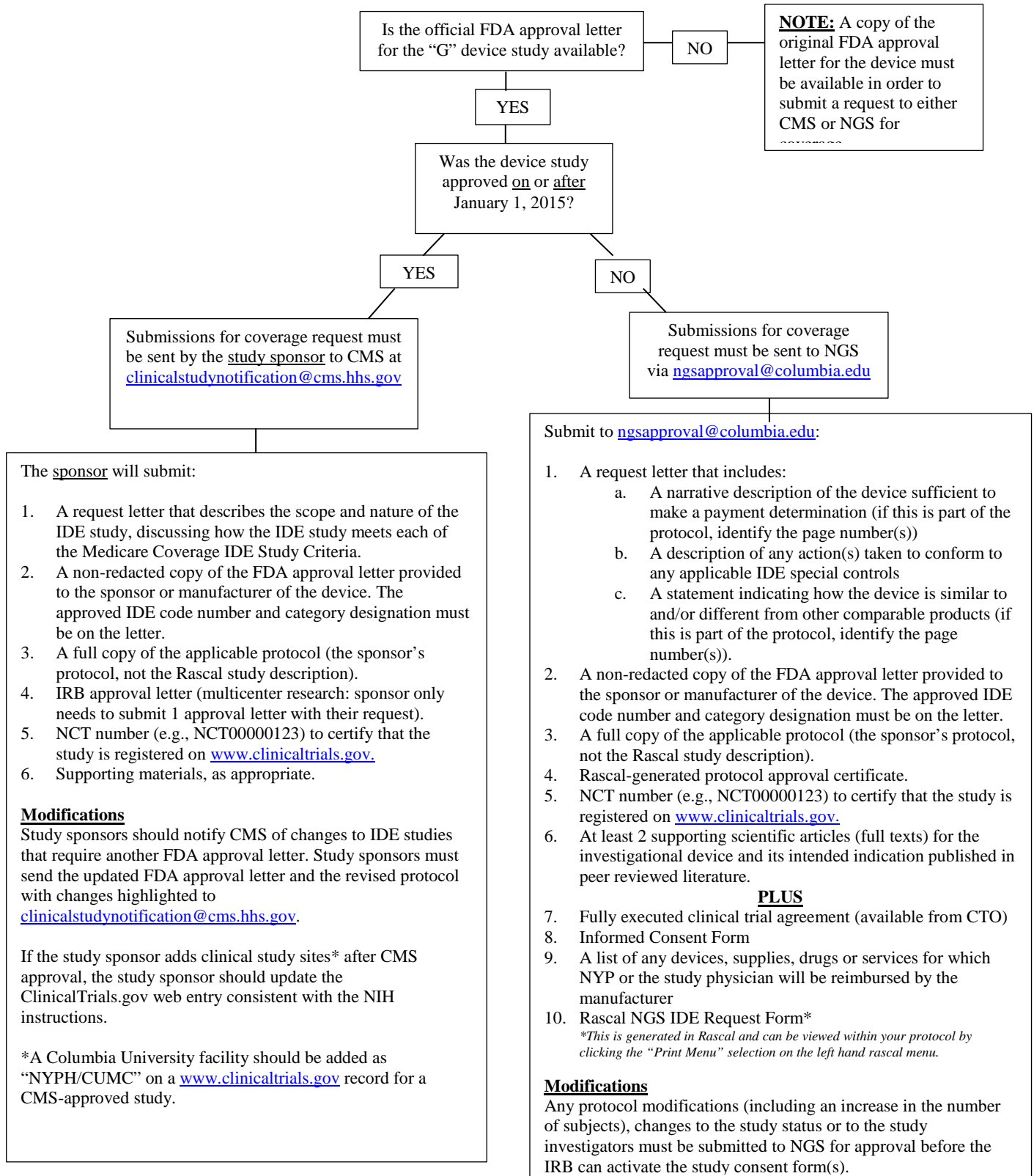
In either case, the consent form for the Covered Study is deactivated until the NGS or CMS determination is obtained and no subjects may be recruited until the consent form has been activated in Rascal.

More information can be found on the CMS website at <http://www.cms.gov/Medicare/Coverage/IDE/index.html>

The following flow chart outlines the foregoing requirements:

Medicare Coverage for Investigational Devices

Investigational device studies under a FDA-issued IDE that begin with the letter “G”, and post-market approval studies or registries of carotid stents, must be submitted to either National Government Services (NGS) or Centers for Medicare & Medicaid Services (CMS) for a coverage decision prior to enrollment of subjects into the study.



E. Submission/Execution

1. Non-Industry Sponsored Clinical Research

Once the grant application, proposal or contract is approved by SPA, it is submitted by SPA to the sponsor in accordance with the requirements of the sponsor's RFA/RFP, program announcement or contract.

2. Industry Sponsored Clinical Research

Once the contract has been finalized, IRB approval has been obtained and all other regulatory requirements have been met, the contract is routed for execution. A contract is executed when it is signed by the following parties: the PI, the University, NYP and the sponsor.

VII. INITIATING A STUDY

A. Introduction

Upon receipt of an award or execution of a contract, the documentation is reviewed and a sponsored project is created in the University's accounting system, Accounting and Reporting at Columbia (**ARC**), so that expenditures that are necessary to make purchases to carry out the terms and conditions of an award or contract can be made and to segregate expenses, create a mechanism for billing sponsors and to generate reports to monitor financial activity. In addition, the sponsor may wish to meet with the research team in preparation of the initiation of the project.

B. Account Set Up and Modifications

The following definitions will help familiarize you with ARC terminology:

Project: A project is created by SPA or the CTO when a sponsored project is awarded and all conditions to ensure compliance with University and sponsor regulations have been met. A project is set up in ARC to capture transactions associated with a specific funding source for the purposes of billing and reporting. A project must have a start and end date and is owned by a specific department. All projects are set up with **activities** to further define a budget period or scope of work. A project number will remain the same for the life of a competitive segment of an award.

Activity: At least one activity is required for each sponsored project in ARC. The activity further defines a budget period or scope of work and helps researchers and administrators manage their funding over the life of a project. For example, a complex project may include separate activities to easily identify separate budget periods and scopes of work or to separate the work of multiple departments contributing to one project. Unlike projects, multiple activities may be created throughout the life of a project, depending on its complexity and any restrictions and carryover funds from year to year.

Account: This term is used in ARC to refer to:

- **Budget account** – a category used for budgeting within activities (for example, “supplies”)
- **Natural account** – the codes used to define detailed expenses or transactions within budget accounts (for example, “laboratory glass ware”)

For more ARC terminology, you can refer to the Finance Glossary at <http://finance.columbia.edu/glossary>.

For a catalogue of online courses and other ARC training sessions, go to <http://finance.columbia.edu/content/finance-training>.

1. Non-Industry Sponsored Clinical Research

Requirements for Setup

SPA sets up all projects for newly awarded or continuing non-industry sponsored projects in InfoEd, which sends the information to ARC. See **Initiating a Sponsored Project Award: Account Setup and Modifications (Chapter VII, Section D)** in the **Sponsored Projects Handbook** for general information on account setup. Your SPA Project Officer or Financial Analyst may contact you during account set up if there are questions concerning your budget, assurances, special terms and conditions or missing documentation.

New project numbers are issued for new awards or competitive renewals. Non-competing renewals, however, may or may not require the creation of new activity numbers from one budget period to the next. If (a) the award requires an annual financial report or (b) the use of any carry forwards requires the prior approval of the sponsor, a new activity will be opened for each non-competing year. This will ensure that the Controller's Office completes an accurate financial report, and that the department does not inappropriately spend carryover funds without sponsor approval.

Setting Up Accounts

The following documents are necessary for account setup. A Financial Analyst will contact you if any of the following items are missing:

New Awards, Competing Awards and Contracts

- Notice of Grant Award (NGA) or fully executed contract
- Copy of original application (if applicable)
- Finalized Rascal PT Record – electronically signed by relevant parties, with up-to-date FCOI disclosure and certification and approval information
- FCOI certification from subcontractors or consultants (if applicable)
- Notice of IRB approval (if applicable)
- Budget - See **Initiating a Sponsored Project Award: Can You Accept This Award? – Reductions in Budget and Rebudgeting (Chapter VII, Section C(2))** in the **Sponsored Projects Handbook** regarding reductions in budget and rebudgeting
- Review of scientific overlap.

Non-competing Multi-Year Awards and Contract Amendments

- NGA or contract amendment
- Updated list of personnel on the study
- Updated Rascal PT Record – electronically signed by relevant parties, with up-to-date FCOI disclosure and certification and approval information
- FCOI certification from subcontractors or consultants (if applicable)
- Copy of Progress Report

- Notice of IRB approval (if applicable)
- Review of scientific overlap

Note that for non-federal sponsors and for subawards, a guarantee letter, a foundation check or an award letter will be required in place of the contract in noncompeting years.

Modifications

Modifications of all non-industry sponsored accounts (including clinical trials) are handled by SPA. Modifications are the result of an amendment or revision to an agreement or NGA and can be driven by the investigator's needs (i.e., a request for additional time or funding) or can originate from the sponsor (change in amount awarded, terms of award, etc.). Account modifications are handled by SPA in the same manner as outlined above for new projects.

2. Industry Sponsored Clinical Research

Industry Sponsored Clinical Trials

Requirements for Setup

The CTO sets up industry sponsored clinical trial projects via the Chartfield Request Form in ARC. All industry sponsored projects are opened for a five-year period. An additional six months to a year may be added to the project period based on the sponsor's guidelines for closeout of the project.

Modifications

Modifications of industry sponsored clinical trials come in the form of contract amendments. A modification can be driven by the investigator's needs or can come from the sponsor, resulting in an additional cost to the study. These modifications could include an added procedure or service or an increase in the number of patients to be enrolled.

When an amendment is needed, it is important to contact the CTO for initial guidance. The assigned CTO Budget Analyst will review the current budget, and request a new Budget Worksheet to ensure that all old and new costs have been captured. Negotiations of the budget and amendment will take place between the CTO and the sponsor. Accounts will be modified based on the terms of amendment.

Industry Sponsored Clinical Research

The account set up process for industry sponsored clinical trials and clinical research is the same as for non-industry sponsored clinical research. See **Non-Industry Sponsored Clinical Research (Section B(1))** above.

3. Advance Accounts

Advance accounts provide PIs with an opportunity to initiate an activity and begin incurring associated expenses prior to institutional acceptance of an award. Advance accounts allow PIs and departments to record and track expenditures and eliminate the need to charge other unrelated accounts. See **Initiating a Sponsored Project Award: Account Setup – Advance Accounts (Chapter VII, Section D(3))** in the **Sponsored Projects Handbook** for a description of the procedures required to set up an advance account.

4. Project Information Notifications (PINs)

Once a project is set up by SPA or the CTO sends a PIN alert by email to the applicable PI and/or DA. See **Initiating a Sponsored Project Award: Account Setup – Project Information Notifications (PINs) (Chapter VII, Section D(4))** in the **Sponsored Projects Handbook** for more information on PINs.

C. NYP

1. Billing

Outpatient

If the study involves outpatient ancillary services (e.g., labs, radiology, MRI) at NYP, after a University account is set up, the CRC must obtain a Financial Class Number and a Patient Serial Number for charges to be made to the study's budget (rather than the patient or the patient's insurer).

A Financial Class Number is the study-specific three-digit number that links NYP Patient Billing to the University account for the study. A Patient Serial Number is the patient-specific eight-digit number that is the link in the NYP billing system from the patient to the Financial Class Number.

The procedures for obtaining a Financial Class Number and a Patient Serial Number, as well as billing for NYP ancillary services, are described in detail in **Annex D**.

Inpatient

If a subject on a research study will be admitted to NYP as an inpatient, the CRC must complete a NYP Inpatient Research Study Information Sheet and certain other documentation depending on the location of the patient and the responsible payor. The required procedures and documentation are described in detail in **Annex D**.

Investigational Devices

If the trial involves a device that requires NGS approval for Medicare billing, see **Preparing for a Study: Review and Finalization of Proposals and Contracts: Approval Process – Additional Approvals and Certifications – National Government Services (NGS) or Centers of Medicare and Medicaid Services (CMS) Determination (Chapter VI, Section D(2))**.

Devices are shipped by the sponsor either to the CRC or NYP. If the device is shipped directly to the CRC, no purchase order (**PO**) is necessary. The CRC should complete a device accountability form provided by the sponsor and/or enter the order in the Device Accountability Log for the study. All packing slips should be kept in the regulatory binder for the study.

If the device is shipped to NYP, a PO is required. If the device is a consignment device, the initial PO will be a “No-Charge” PO. If the hospital is required to pay for the device, the PO will be a “Bill Only” PO. The PO is handled by Procurement and Strategic Sourcing (**PSS**) at NYP.

When you are requesting a PO, send an email to the Procurement Director, Clinical Goods and Services at PSS (current contact: Anand S. Joshi at asj9001@nyp.org) with the following information:

- Type of device (equipment or implantable)
- IDE Number and investigators involved in the study
- Whether sterilization is required
- Whether operating room inservices are required prior to use.

In addition, CRCs must contact the Director of Peri-operative Services to schedule nursing/staff training regarding research related intraoperative devices. The training must be conducted at least 72 hours prior to the scheduled procedure.

2. Medical Equipment

NYP has a Medical Equipment Management Plan that covers all equipment used in hospital space, including general patient care equipment, clinical laboratory equipment and radiology equipment. All purchases of new medical equipment must follow NYP’s capital approval process that includes an evaluation by NYP’s Department of Biomedical Engineering to determine the level of maintenance appropriate for the type of equipment. During the initial inspection, the equipment is assigned and tagged with a unique Biomed Asset Number that is used in all maintenance actions. A preventive maintenance (**PM**) sticker attesting to the equipment’s safety and performance is also placed on the equipment next to the Asset Number tag. If the equipment does not require preventive maintenance, a sticker indicating “Safety Check Performed, No PM Required” should be placed on the equipment. Equipment that is overdue for inspection pursuant to its preventive maintenance schedule should not be used for patient use.

D. ClinicalTrials.gov

On September 16, 2016, HHS issued a new regulation (the **2016 HHS Final Rule**) and the NIH issued a new complementary policy (the **2016 NIH Policy**) to increase the availability of information about clinical trials via ClinicalTrials.gov. The 2016 HHS Final Rule has been codified at 42 CFR 11 and the 2016 NIH Policy has been published in the NIH Guide for Grants and Contracts at <https://grants.nih.gov/funding/searchGuide>. The 2016 HHS Final Rule becomes effective on January 18, 2017 and has a compliance date of 90 days after the effective date. The NIH 2016 Policy becomes effective on January 18, 2017.

Currently, HHS requires that the following clinical trials (**Applicable Clinical Trials**) be registered in ClinicalTrials.gov:

- Phase 2, 3 and 4 interventional studies;
- Studies involving drugs, biological products and medical devices regulated by the FDA; and
- Studies having at least one site in the United States or one of its territories or are conducted under an IND or IDE.

Excluded studies include Phase 1 drug trials, small feasibility/pilot studies of devices, behavioral interactions and non-interventional (observational) clinical research. The 2016 HHS Final Rule does not change the definition of Applicable Clinical Trial.

In addition, the 2016 Final Rule expands the requirements for submission of results for Applicable Clinical Trials. Information with respect to results must be submitted by all ACTs that are subject to the registration requirements, regardless of the approval status of studied drug, product or device. This requirement only applies to Applicable Clinical Trials with a primary completion date on or after January 18, 2017.

The NIH does not currently have a policy on registration of clinical trials. The 2016 NIH Policy applies to all clinical trials funded in whole or in part by the NIH, regardless of the study phase or type of intervention or whether they are subject to the 2016 HHS Final Rule. In addition to the trials covered by the 2016 HHS Final Rule, the 2016 NIH Policy applies to all other trials funded by the NIH, including Phase 1 trials of drug and biological products, small feasibility studies of device products and clinical trials of behavioral, surgical and other types of health and medical interventions.

Currently, HHS provides that registering the trial and providing the data with respect to results are the responsibilities of the **Responsible Party**, which is:

- The study sponsor (i.e, the holder of the IND or IDE); or
- The PI responsible for conducting the study, analyzing the data and publishing the results, if designated by the sponsor.

The 2016 HHS Final Rule does not change the definition of Responsible Party and the 2016 NIH Policy uses the same concept, but provides that the awardee or PI is responsible for meeting the requirements of the 2016 NIH Policy. At the University, the

sponsor or PI is assumed to be the responsible party for all clinical trials that are initiated by a University investigator. An exception would be when the University is a subrecipient under a prime award made to another academic institution; the sponsor of the PI at the other institution would be the responsible party for registration purposes. The 2016 NIH Policy requires that applicants for NIH funding submit a plan outlining how they will comply with the clinical trial information dissemination expectations of the Policy.

There are two types of information required to be entered into ClinicalTrials.gov:

- **Registration Information:** descriptive, recruitment, location, contact and administrative information. This information is required to be submitted no later than 21 days after the first subject is enrolled.
- **Results Information:** summary results information that includes scientific information (i.e., participant flow, baseline characteristics, outcome measures and statistical analyses) and administrative information (i.e., point of contact to obtain more information about reported results). Adverse event reporting is also required and includes serious adverse events and other adverse events that exceed a frequency threshold of 5% within any arm of the clinical trial. This information should be reported within one year of completing data collection for the pre-specified primary outcome.

The 2016 HHS Final Rule adds the requirement that all-cause mortality results be reported, with the number and frequency of deaths due to any cause by arm.

Both the 2016 Final Rule and the 2016 NIH Policy impose strict timing requirements for registration and results reporting. In general, a Responsible Party must register an Applicable Clinical Trial (or other clinical trial subject to the 2016 NIH Policy) no later than 21 days after enrolling the first participant. Registration consists of submitting the Registration Information described above.

On the other hand, a Responsible Party must submit the Results Information described above no later than one year after the primary completion date of the clinical trial. The **Primary Completion Date** is the date on which the final subject is examined or receives an intervention for the purpose of collecting data for the primary outcome measure.

In addition, all submitted information must be updated at least once a year, although the following fields must be updated within 30 calendar days after the change:

- Establishment of a nonproprietary name
- Status of availability of an expanded access program
- Overall recruitment status
- Study start date
- Individual site status for each site
- IRB status

- Primary Completion Date and study completion date
- Responsible Party and contact information
- Protocol amendments that require changes to be communicated to subjects.

One field---the approval or clearance status of a device product not approved or cleared by the FDA---must be updated within 15 days after the change.

For any clinical trial subject to the 2016 Final Rule or the 2016 NIH Policy, the following statement must be reproduced word for word in the applicable informed consent documents:

“A description of this clinical trial will be available on <http://ClinicalTrials.gov>, as required by U.S. law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.”

For further information see:

<https://www.nih.gov/news-events/summary-hhs-nih-initiatives-enhance-availability-clinical-trial-information>

<https://www.nih.gov/news-events/summary-table-hhs-nih-initiatives-enhance-availability-clinical-trial-information>

<https://prsinfo.clinicaltrials.gov/FinalRuleChanges-16Sept2016.pdf>

E. E-Verify

Certain federal contracts include a requirement that all employees (existing and new) working on such contracts undergo additional employment authorization validation through a federal system called E-Verify. This requirement applies to academic personnel (faculty, officers of research, officers of the libraries and student officers) and administrative staff (including casuals).

See **Initiating a Sponsored Projects Award– E-Verify (Chapter VII, Section F)** in the **Sponsored Projects Handbook** for further information.

F. Preparation for Initiation

1. Investigator Meeting

Many sponsors of clinical trials hold investigator meetings in order to familiarize site personnel with the protocol and specific requirements of the study. Investigator meetings afford an opportunity to meet CRAs, medical monitors and other sponsor personnel, who

may serve as valuable resources in the future. Investigator meetings also provide an opportunity to ask questions about the protocol and study requirements.

The agendas of investigator meetings often include GCP review, regulatory compliance review, protocol overview, Investigator's Brochure overview, discussion of pre-clinical study data, discussion of inclusion/exclusion criteria, electronic data capture training (if applicable), and an overview of laboratory shipping requirements (if applicable). Investigator meetings also afford an opportunity to meet vendors selected by the sponsor to administer aspects of the clinical trial.

Site Initiation Visit

Industry sponsored multi-center clinical trials often have site initiation visits (**SIVs**). The SIV occurs when the protocol has been approved by the IRB, the contract is executed and the test article has been shipped to the site. At the SIV, the CRA or sponsor representative may review the protocol requirements in detail with the CRC and PI. They may also review the following items:

- GCP requirements
- Regulatory documentation
- Investigator obligations
- Informed consent procedures
- Study monitoring plans
- IRB reporting requirements
- Sponsor reporting requirements
- Study record storage requirements
- Procedures for enrolling patients
- Procedures for patient withdrawals
- Study treatment procedures
- Test article administration
- Management of unanticipated problems, adverse events and serious adverse events
- CRF completion instructions
- Test article control procedures.

In addition, the CRA may visit the Research Pharmacy to confirm test article receipt. A thorough review of the regulatory binder will also take place.

2. Study Documentation

It is important for the CRC to set up and maintain study specific information on an ongoing and timely basis. A well managed set of files is critical for efficient trial management and regulatory compliance. For clinical trials, there are generally three types of files used: a regulatory binder, a financial documents file and patient/subject files. For other clinical research, the methodology for maintaining the study documentation may differ.

The Regulatory Binder

The regulatory binder is the primary organizational system for regulatory documents and must be constructed prior to the commencement of the clinical trial. CRCs may create a regulatory binder upon receipt of a protocol and add documentation as it accrues. Some documents in a regulatory binder are sponsor specific and differ between protocols, while other components are standard. Industry sponsors sometimes provide the regulatory binder or indicate which items they expect to be included in the binder. Because you will not have this guidance for non-industry sponsored clinical trials, it is important for the PI and the CRC to be proactive in compiling and maintaining the regulatory binder for such studies.

The following is a list of typical documents found in a regulatory binder. The documents are described in more detail in various sections of this Handbook. The CRC should keep the file current and up-to-date by adding any amendments or modifications to the binder during the course of trial. All versions should be retained.

- Study protocol signed and dated by the PI
- Study protocol (stand alone version or Rascal Data Sheet)
- Information given to study subjects as approved by the IRB
 - Informed consent form (including translations) with the IRB approval stamp
 - HIPAA authorization or IRB waiver of authorization
 - Advertisement
 - Brochures or other information
- Evidence of other required approvals, as applicable
 - Biological safety
 - Irving Institute
 - PRMC
 - Radiation safety
- Signed originals of current CVs of the PI, other investigators and the CRC, if applicable, and, if required by the sponsor, dated within the last two years
- Medical licenses
- Training certificates, as applicable
 - Biological Safety/Bloodborne Pathogens/Infection Control
 - HIPAA
 - Human Subjects Protection
 - Radiation Safety
 - Shipping Biological (Infectious and Potentially Infectious) Materials
 - Shipping with Dry Ice, Exempt Specimens and Excepted Quantities of Dangerous Goods
- IRB roster listing all members of the IRB reviewing the study and titles
- Delegation of Authority Log – this document identifies all personnel involved in the study, their specific responsibilities, the time period for which the authority is delegated and their signatures and initials, and is signed and dated by the PI. A sample of a Delegation of Authority Log can be found in **Annex F**.

- Laboratory certifications and licenses to evidence competence of laboratories used in the study
- Normal reference ranges of each laboratory
- IRB correspondence
- Sponsor correspondence
- Other relevant correspondence
- Screening Log
- Enrollment Log
- Adverse Event/Serious Adverse Event Log
- Unanticipated Problem, Adverse Event and Serious Adverse Event Reports
- Close-out report

For studies involving an investigational drug or device, certain additional documents are needed:

- Form FDA 1571 (IND trials)
- Form FDA 1572 (IND trials) or Investigator Agreement (IDE trials)
- Investigator’s Brochure – This document provides information about the drug or device and is produced by the sponsor.
- Instructions for labeling and handling investigational products
- Certificate of analysis – This certificate documents identity, purity and strength of investigational product
- Data and safety monitoring plan
- Log of monitor visits and all monitoring reports
- Shipping records for investigational products
- Drug accountability log (unless maintained by the Research Pharmacy)
- Device accountability log.

Financial Documents File

Financial documents should be maintained separately from the regulatory binder, as they should not be available for review by the FDA during inspections. See **Audits: FDA Inspections (Chapter XVI, Section D)**. The following are some of the documents that might be included in this file:

- NGA and other documentation relating to grants
- Copy of executed CTA. The original should be kept in the CTO or SPA files.
- FCOI Disclosure Forms. As discussed in **Review and Submission of a Sponsored Project Proposal: Additional Approvals and Certifications – Financial Conflicts of Interest (FCOIs) (Chapter VI, Section E(1))** in the **Sponsored Projects Handbook**, all personnel on a research team are required to complete and submit an annual financial interest report in Rascal at the time of the grant application or contract negotiation and updated when necessary to reflect any changed circumstances that could give rise to a conflict of interest. In addition, all key personnel are required to submit a protocol-specific financial conflict of interest report at the time a new or renewing protocol is submitted for

IRB review. Additional information is available at the website below:
http://www.columbia.edu/cu/compliance/docs/conflict_interest/resources.html

- Copies of NYP blue bills
- DARTs reports
- Patient reimbursement documentation
- StudyManager™ dashboards
- Reconciliation of study expenses

Patient/Subject Research File

This file should be maintained for each study subject and should include patient data, forms and correspondence that could include the following:

- Original informed consent form and HIPAA authorization or IRB waiver of authorization
- Medical records
- Correspondence with the subject
- Queries
- Dosing or randomization documents
- Completed, signed and dated CRFs.

VIII. WORKING WITH STUDY SUBJECTS: RECRUITMENT AND ENROLLMENT

A. Introduction

The first contact that a CRC will have with a study subject is during the recruitment and enrollment period as the study is starting up. Although recruiting the maximum number of subjects to a study is always a goal, the process must be free of any possible coercion or undue influence. Plans for subject recruitment must be approved by the IRB prior to the initial approval of the protocol, and at each continuing review.

B. Finding Subjects

Current University policies limit acceptable recruitment methods for patients to minimize use of private information by anyone other than those individuals who have legitimate access to the patient and his/her PHI. Acceptable methods include the following:

- A patient's treating physician (i.e., a clinician with whom the patient has a relationship predating introduction of the research) introduces the study to the patient and obtains and documents permission from the patient to provide his/her contact information to the researcher.
- A patient's treating physician introduces the study to the patient and provides the patient with written material about the study so that the patient can contact the researcher directly to obtain further information about the study.
- The patient obtains recruitment material from the treating physician's office or from a public area (e.g., bulletin board), learns about the study through an advertisement or finds the study on a website that provides a data base of studies applicable to particular illnesses and contacts the researcher directly to obtain further information.

Columbia researchers are generally not permitted to initiate contact with a potential subject directly unless the subject is already a patient of the researcher.

The FDA has published guidelines in the FDA Information Sheets under "Recruiting Study Subjects." See <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>.

See discussion of use of patient data for recruitment under HIPAA in **Working with Study Subjects: Informed Consent: Other Consents - HIPAA (Chapter IX, Section G(1))**.

C. Clinical Data Warehouse

The Clinical Data Warehouse (CDW) is maintained by NYP and contains information on every NYP patient since 1996. Investigators may query the CDW and receive a report in the format specified. The CDW can be accessed through the Biomedical Informatics Resource of the Irving Institute. See http://irvinginstitute.columbia.edu/resources/bio_info.html.

Note that requests to use individual patient or electronic health record data from NYP, CUMC or Cornell data storage systems must be approved by the Tripartite Request Assessment Committee (TRAC) of NYP, CUMC and Cornell prior to its use. See <https://webapps.nyp.org/trac/>.

D. Advertising

1. General

Because advertising is considered to be part of the informed consent process, all materials that are intended to be used to encourage a potential subject to consider volunteering for a research study must be approved by the IRB. For FDA-regulated research, see also FDA Information Sheet “Recruiting Study Subjects” at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm>.

The IRB defines advertising as any research-related information that will be seen or heard by a potential subject before he/she has read and signed a consent form for the study. This means that advertising may include:

- Printed items in newspapers, magazines, flyers, posters, etc.
- Radio announcements
- TV productions or commercials
- Video presentations
- Internet postings
- Informational brochures
- Letters to potential subjects
- Imprinted items (notebooks, bags, etc.)

The IRB reviews the text of any written materials as well as audio and video advertising materials. Both scripts and the actual audio or video tape must be submitted to the IRB. See <http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>.

Approved recruitment material will be electronically stamped with the IRB protocol number and the dates of approval and expiration. For protocols determined to be exempt, the stamp will include the date the exempt determination was made. In instances in which the material is difficult to stamp, the IRB may stamp one copy for documentation and accept a process whereby the stamped copy is returned by the researcher for documentation of IRB approval, but the actual documents may be produced and distributed without a stamp on each copy.

2. Non-English Speaking Subjects

The informed consent process with respect to potential subjects for whom English is not their primary language is described in detail in **Working with Study Subjects: Informed Consent: Special Situations – Non-English Speaking Subjects (Chapter IX, Section F(1))**. Please note that recruitment materials such as flyers must be translated into the applicable foreign language

and the translation certified by an acceptable translator and approved by the IRB prior to use. See <http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>.

E. Enrollment and Accrual

1. Prescreening

Certain information may be obtained to determine the eligibility of potential subjects before obtaining written informed consent to participate in the study. Prescreening may be done in person or by telephone. Prescreening may also be done by chart review; however, it is important to have the appropriate permission and documentation for this. See **Working with Study Subjects: Informed Consent (Chapter IX)** for further discussion of informed consent.

Information that the CRC may gather during prescreening includes whether or not the potential subject meets the inclusion/exclusion criteria detailed in the protocol and whether or not the potential subject would be able to comply with the requirements of the protocol, such as multiple study visits to the research site.

If the subject appears to satisfy the inclusion criteria (and does not meet any exclusion criteria), the CRC may schedule the potential subject for a visit in order to obtain informed consent and perform screening procedures, as per the protocol.

2. Screening and Enrollment

Screening of patients determines research eligibility and may only be done after obtaining written informed consent from the subject. See **Working with Study Subjects: Informed Consent (Chapter IX)** for further discussion of informed consent. Any subject who has signed an informed consent form is considered to be **enrolled** in the study.

Screening may include various clinical procedures, such as a medical history, physical exams and laboratory tests. Withdrawal from non-study medicine (“wash out”), if done in anticipation of participation in a study, constitutes screening. Procedures that are to be performed as part of the practice of medicine and that would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research. When a physician-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

The final decision on eligibility is made by the PI in many cases. If the study is an industry sponsored multi-center study, the final decision on eligibility is made by the PI in conjunction with the sponsor.

3. Accrual

When a subject has successfully been screened for a study, he/she is considered to be **accrued** in the study. Accrual procedures differ by protocol. Any exception to the inclusion/exclusion criteria to accrue a patient should be approved by the sponsor and the IRB and well documented.

4. Documentation

It is essential that the CRC maintain a Screening/Enrollment Log in measuring enrollment, screening and accrual progress that are required by GCP. A sample Screening/Enrollment Log can be found in **Annex F**.

In many cases, it may be helpful to create enrollment packets that include the documents needed to screen and enroll patients. The packets could contain the following documents:

- Inclusion/Exclusion Criteria checklist (a sample checklist can be found in **Annex F**)
- Study procedures checklist
- Screening forms
- Patient forms (informed consent, HIPAA authorization, medical release, tax form)
- Educational materials
- Instructions
- Registration forms
- Prescriptions
- Vouchers
- Laboratory requirements
- Specimen labels
- Questionnaires
- Evaluation forms

It may also be helpful to develop a set of patient instructions to be given to each subject that could include:

- Name of medication and indication
- Medication dosage and schedule
- Any special storage instructions
- List of medications that should or should not be taken concurrently
- List of foods that should be avoided
- Reminders to return all medication bottles or blister packs, even if used.

5. Registration of Subjects in iNYP

In an effort to ensure the safety of research subjects, all clinical trial subjects, including those in non-industry sponsored clinical trials as well as those in industry sponsored trials, will be registered in StudyManager™ which is linked to iNYP, NYP's clinical data site. The registrations will indicate to clinical teams that a patient is enrolled in a clinical trial. The NYP Medical Record Number will serve as the link between the research record in StudyManager™ and the patient's medical record at NYP.

On a nightly basis, the most recently approved study protocol and IRB approved consent form(s) are transmitted from Rascal to the participant's medical record in iNYP, based on documentation in StudyManager™ that the patient is enrolled in an IRB-approved clinical trial.

IX. WORKING WITH STUDY SUBJECTS: INFORMED CONSENT

A. Introduction

Columbia requires that legally effective informed consent be obtained from every subject in a research project or the subject's legally authorized representative unless the requirement is waived by the IRB or the research is exempt from IRB review. Legally effective informed consent has two primary requirements:

- The investigator or his/her designee explains all of the elements of informed consent as provided in the federal regulations (see **Elements of Informed Consent (Section B)** below); and
- The prospective participant understands all of such elements of informed consent.

The foregoing requirement applies to all research involving human subjects, including behavioral, social science, epidemiological and biomedical research.

Legally effective informed consent is not fully defined by federal regulations and therefore, state law must also be considered. Hence, Columbia's policy for obtaining legally effective informed consent for participation in human subjects research is based on HHS regulations ([45 CFR 46](#)), FDA regulations ([21 CFR 50](#)), New York State law ([Article 24A, Sections 2440 & 2442](#)), GCP guidelines ([ICH E6 \(R2\) Step 2, 11 June 2015](#)) and the ethical principles articulated in the Belmont Report.

B. Elements of Informed Consent

1. Federal Regulations

Both HHS ([45 CFR 46.116](#)) and FDA ([21 CFR 50.25](#)) regulations require that each subject in research provide consent in a process that provides an understanding of the following eight elements of consent:

- The purpose of the research and expected duration of the subject's participation, the procedures that will be followed and identification of any procedures that are experimental;
- Any reasonably foreseeable risks or discomforts;
- Benefits to subjects or others that may reasonably be expected;
- Appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (for greater than minimal risk research);
- The extent, if any, to which confidentiality of records identifying the subject will be maintained;

- Whether any compensation will be provided 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 (for research greater than minimal risk);
- Whom to contact for questions regarding the research, research-related injuries and rights as a research subject; and
- That participation is voluntary; refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled and participation may be discontinued at any time without any such penalty or loss.

The federal regulations also provide additional elements of informed consent that should be considered. When appropriate, one or more of the following elements of information should also be provided to each subject:

- 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;
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
- Any additional costs to the subject that may result from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and
- The approximate number of subjects involved in the study.

Further details of the elements of consent can be found at:

http://www.cumc.columbia.edu/dept/irb/policies/General_requirements_for_informed_consent.html.

The federal regulations require that an investigator seek consent only under circumstances that provide the prospective participant or his/her legally authorized representative with sufficient opportunity to consider whether or not to participate in the research and that minimize the possibility of coercion or undue influence. The information that is given to the participant or such representative should be in language understandable to the participant or his/her representative. Further details about enrollment of non-English speaking subjects can be found in **Special Situations: Non-English Speaking Subjects (Section F(1))** below.

2. Informed Consent Forms

As indicated in **Preparing for a Study: IRB Approval (Chapter V)**, the IRB requires that the consent form be attached to the protocol that is submitted to the IRB. Rascal contains a number of templates for sample text within the Consent Builder and on the IRB website.

A consent form must contain information on the elements of consent described in **Elements of Informed Consent: Federal Regulations (Section B(1))** above. However, the elements must be presented in simple lay language that would be understandable to an 8th grader. Sentences should be short and in the active voice. Exculpatory language must never be used.

See **Initiating a Study: ClinicalTrials.gov (Chapter VII, Section (D))** for specific language about ClinicalTrials.gov that must be included in an informed consent form for an Applicable Clinical Trial. For FDA Guidance Document on Informed Consent Form Elements, see <http://www.cumc.columbia.edu/dept/irb/policies/documents/InformedConsentFinalRule-QAFeb2012-Final.pdf>.

3. Exempt Research

Exempt research is not subject to the federal regulations and therefore informed consent is not required for such research. However, in the spirit of the principles of the Belmont Report, the IRB strongly recommends that informed consent be obtained for certain exempt studies. For exempt studies that allow for direct interaction between the investigator and human subjects, participants should minimally be informed of the following: that the activity is research, the procedures that are involved in the study, the nature of the risks (e.g., little, if any expected inconvenience or harm), that participation is voluntary and that they may withdraw from the study at any time. Benefits to the participant or others, plans for ensuring confidentiality, and contact information for the investigator should also be provided when relevant. The information may be communicated orally and when practicable should be supported with an information sheet.

C. Consent Process

In obtaining legally effective informed consent from a prospective participant for non-exempt research, the individual must have both the capacity to make decisions and appropriate opportunity to consider all information relating to participation in the research study. The PI is responsible for ensuring that legally effective consent is obtained from each participant prior to enrollment of the individual in the study. Furthermore, legally effective consent must be obtained prior to procedures and assessments (e.g., screening or diagnostic tests, surveys, etc. required by the study) that are conducted to determine eligibility for enrollment in the study.

For research studies conducted with inpatients in a hospital, the physician of record for care of the patient during the hospitalization must approve the enrollment of his/her patient in the study if medical intervention is involved. Once the physician of record has approved enrollment, he/she or another treating physician may inform the patient of the research study and ask if he/she is interested in participating.

The responsibility to obtain legally effective consent extends to the PI's selection of designees who are authorized to obtain consent. In selecting an appropriate designee to obtain informed consent, the PI should consider the nature of the research study and the expertise of the designee, as well as institutional and regulatory requirements to ensure that informed consent will be obtained appropriately from each participant.

D. Documentation

The consent process must be documented by: (1) obtaining the signature of the prospective participant on the IRB-approved informed consent document(s), unless this requirement has been waived by the IRB, and (2) documenting the process itself in the research records as noted below. The name of the person obtaining consent and the date that consent was obtained should be documented on the consent form.

For minimal risk research, the signed IRB-approved informed consent document generally serves as adequate documentation of the consent process unless otherwise stipulated by the IRB for a specific research activity. For research activities approved by the IRB with only verbal consent (i.e., waiver of the documentation of informed consent), the research records should document that verbal consent was obtained in accordance with IRB requirements. At a minimum, the name of the person obtaining consent and the date on which consent was obtained should be documented.

For all research that is greater than minimal risk, documentation of the informed consent process should be provided in the research records. Such documentation, when appropriate, should also include other relevant information such as resolution of substantive questions raised by the participant, assessment of the capacity to provide consent, or how undue influence was effectively managed and eliminated.

For clinical research studies that are greater than minimal risk or that involve a participant who is an inpatient at NYP, the original of the informed consent document should be kept in the subject's research file, with a copy of the signed document included in the subject's medical record. If patients are hospitalized at the time of enrollment, the time the consent was obtained should also be documented on the consent form and in the patient's medical record.

If verbal consent is obtained from a hospitalized patient, documentation of the discussion with the patient and a copy of the IRB form approving verbal consent must be included in the hospital medical records.

E. Exceptions

1. Waiver of Consent

The IRB may approve a consent procedure that does not include or alters some or all of the elements of informed consent, or may waive the requirement to obtain informed consent if all of the following criteria can be appropriately satisfied:

- the research involves no more than minimal risk to the subjects;
- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration; and

- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

For consideration of a waiver or alteration of the requirement to obtain informed consent, the investigator should include in the submission to the IRB justification for each of the above criteria.

Waiver of the requirement to obtain informed consent may also be requested by the investigator for a research or demonstration project if:

- Such project will be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
 - public benefit or service programs;
 - procedures for obtaining benefits or services under those programs;
 - possible changes in or alternatives to those programs or procedures; or
 - possible changes in methods or levels of payment for benefits or services under those programs; and
- The research could not practicably be carried out without the waiver or alteration.

2. Waiver of Written Documentation of Informed Consent

The IRB may waive the requirement for the investigator to obtain a signed consent form, for some or all subjects in a study, if it finds either:

- That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

For consideration of a waiver of the requirement to obtain written documentation of informed consent (e.g., a signed consent form), the investigator should include in the submission to the IRB justification for the relevant criterion found above.

In cases in which the documentation requirement is waived, the IRB may require that the investigator provide participants with a written statement regarding the research.

3. Emergency Waiver

There are two situations in which exceptions to consent may be made for patients using investigational products: an individual exception for the emergency use of a test article in a single person and the emergency research exception that involves studies in which, because of exceptional circumstances, it is generally not feasible to obtain consent before treatment (e.g., studies involving trauma patients).

Individual Emergency

It is possible that in certain life threatening circumstances, a physician may treat a patient with an investigational product without obtaining informed consent. Such use is considered to be an emergency clinical use and FDA requirements for research use do not apply. As a result, data collection for research purposes is not permitted other than for reporting to the sponsor or the FDA.

Emergency use without informed consent is permissible only when (a) the subject is in a life threatening situation necessitating the use of the test article, (b) the subject is unable to give consent because he/she is unable to communicate, (c) time is not sufficient to obtain consent from the subject's legally authorized representative and (d) there is no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the subject's life.

Both the investigator and a physician who is not otherwise participating in the study must certify in writing that the foregoing requirements have been met. If time is not sufficient to obtain an independent determination, the investigator may make the decision alone and within five working days, obtain the concurrence of an independent physician that the criteria for waiver of informed consent were met ([21 CFR 50.23\(a\) and \(b\)](#)). In either case, any documentation that was not provided prior to the use of the test article is required be submitted to the IRB within five working days after the use of the test article. This should be done by email to irboffice@columbia.edu.

If emergency use of an investigational product is being considered, the physician is encouraged to contact the HRPO office immediately, as the HRPO can serve as a facilitator for shipment of the product and initiation of the monitoring process. In some cases, the manufacturer will require documentation from the HRPO, on behalf of the IRBs, that it is aware of the proposed use. In all cases, the manufacturer or sponsor must be notified of all emergency use situations and an emergency IND must be obtained from the FDA, which has procedures in place to expedite the review of such applications.

Emergency Research Studies

In some studies, obtaining informed consent from a study subject prior to his/her participation may not be possible and time may not permit obtaining consent from the subject's legally authorized representative.

Waivers of consent for planned emergency research must be approved in advance of the study by the IRB following review of the community consultation procedures that have been or will be conducted. Documentation that the criteria for waiver codified at [21 CFR 50.24](#) have been met must be included with the request, as well as the affirmation from a licensed physician who is not associated with the research project (who may or may not be a member of the IRB).

The IRB will ensure that there are procedures in place to inform, at the earliest feasible opportunity, each subject that he/she has been enrolled in the research. If the subject remains incapacitated, the investigator must inform a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member. The following information must be communicated:

- The subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document; and
- The fact that his/her or the subject's, as applicable, 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 informed about the clinical investigation, and the subject's condition improves, the subject should also be informed as soon as feasible.

If a subject is entered into a clinical study with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical study should be provided to the subject's legally authorized representative or family member, if feasible.

The IRB may require additional protections for subjects in an emergency research consent waiver study as appropriate.

4. Surrogate Consent

If an adult subject of a study lacks the capacity to provide his/her consent, either because of mental impairment or because of the nature of the illness (e.g., a stroke), surrogate consent may be obtained in some situations. Use of surrogate consent must be approved by the IRB prospectively during review of a protocol or modification of a protocol.

The IRB will generally consider the use of surrogate consent for research that: (a) provides the prospect of direct benefit to subjects who lack capacity or (b) studies disorders, conditions or factors that affect individuals who lack capacity when the research is minimal risk, with or without the prospect of direct benefit, and the research could not otherwise be conducted on subjects who have capacity.

The submission to the IRB must include details of how the investigator will verify the authority of the individual to serve as the legally authorized representative designated to provide surrogate consent and how the capacity of the subject will be assessed.

Subjects who appear to lack capacity must have the assessment of capacity made by a licensed physician in accordance with standard practice and applicable state law. In general, the determination that the subject lacks capacity may not be made by the study investigators or study staff. For a given study, the IRB may approve an exception to this prohibition. For an exception

to be granted by the IRB, the investigator must submit a specific request for such an exception that includes a justification and written plan for assessment of capacity.

For human subjects research conducted in New York State, the following persons are considered legally authorized representatives who may act as a surrogate:

- A court-appointed legally authorized representative/guardian or guardian authorized to decide about health care pursuant to Article 81 of the Mental Health Law;
- An individual who is designated as a representative/agent through a health care proxy that is properly executed. For a health care proxy to be effective, it must have been signed at a time when the subject has decision making capacity. The subject's wishes, if any, with regard to research as expressed in the health care proxy govern (e.g., prohibiting all research or permitting only research which may provide a direct benefit); or
- If an individual who satisfies the requirements of either paragraph above does not exist, surrogate consent may be obtained from a person on the following list from the class highest in priority who is reasonably available and willing and competent to act:
 - the spouse (if not legally separated from the subject) or the domestic partner;
 - a son or daughter 18 years of age or older;
 - a parent;
 - a brother or sister 18 years of age or older; or
 - a close friend (meaning a person 18 years of age or older who has maintained such regular contact with the subject as to be familiar with the subject's activities, health and beliefs).

Such a person listed above may designate another person on the list to be a surrogate provided that no one in a class higher in priority than the person designated objects in a timely fashion.

For protocols that may provide direct benefit to subjects in emergent, life-threatening situations, the IRB may approve a hierarchy of succession that permits a surrogate listed above to provide consent if a representative/agent through a health care proxy exists but is not reasonably available.

For human subjects research conducted in other states, requests for the use of surrogate consent will be considered by the IRB in accordance with applicable state law.

If a subject previously determined to lack capacity to consent regains capacity during the study, the investigator must obtain the consent of the individual for the remaining part of the study. The consent process must disclose all research procedures performed to date and allow the individual an opportunity to continue in or withdraw from the study. The subject must sign the IRB-approved consent document and the research record should document what research procedures were already performed or remain to be performed.

The submission to the IRB must include details of how the investigator will verify the authority of the individual to serve as the surrogate. See http://www.cumc.columbia.edu/dept/irb/policies/documents/Informed_Consent_Policy102610FinalDraft.pdf.

F. Special Situations

1. Non-English Speaking Subjects

In order to obtain informed consent from any prospective study subjects who are not fluent in English (**Non-English Speaking Subjects**), special requirements must be met. There are two possible scenarios: (a) when the subject population is anticipated to include a significant number of subjects who are not fluent in English, but are fluent in any single language other than English and (b) when Non-English Speaking Subjects are not anticipated in a study, but are individually encountered.

When Non-English Speaking Subjects Are Anticipated

In this situation, the IRB requires a certified translation of the English version of the study's consent document (**Long Form Consent Document**) **into the language that is anticipated after the English version has been approved by the IRB**. This translation must be given to the potential subject during the consent process.

When Non-English Speaking Subjects Are Not Anticipated

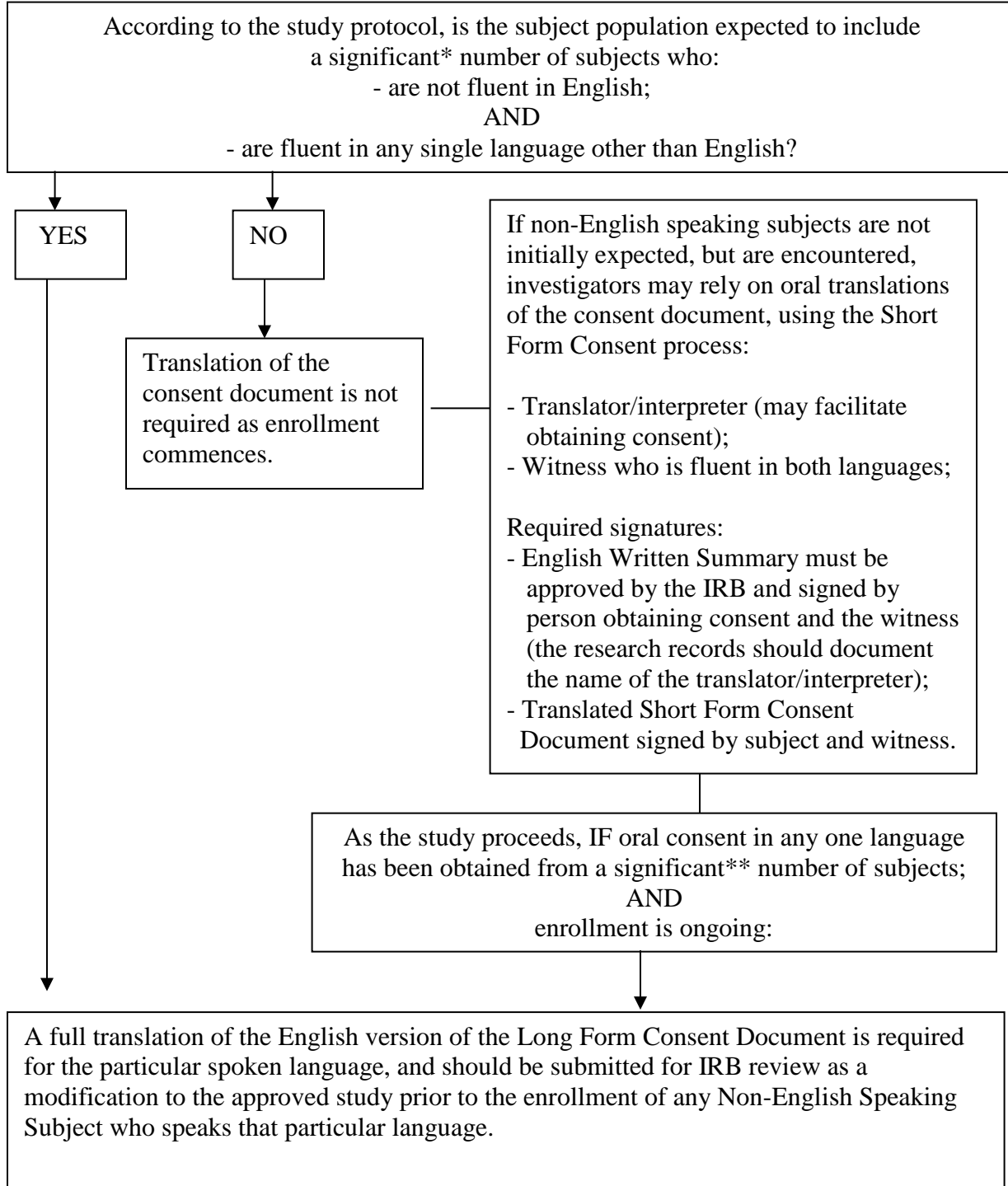
In this situation, investigators may rely on an oral translation of the approved consent document. The following procedures must be followed:

- The English version of a short form consent document (the **Short Form Consent Document**) must be translated into a language understandable to the Non-English Speaking Subject. The Short Form Consent Document is a one page form that identifies the PI and title of the research study, and summarizes the elements of informed consent, but does not describe any specific information about the research study. Several pre-approved translations of Short Form Consent Documents as well as an English sample are posted on the IRB website for immediate use in the event that an investigator unexpectedly encounters a Non-English Speaking Subject. <http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc>. If there is no translation of a Short Form Consent Document in a particular language on the IRB website, a translated Short Form Consent Document, together with the certification of translation, must be submitted to the IRB through Rascal as a protocol modification and approved by the IRB prior to it being used to enroll Non-English Speaking Subjects who speak that particular language.

- A written summary in English of the information provided in the Long Form Consent Document (a **Written Summary**) must be approved by the IRB and provided to each Non-English Speaking Subject. The IRB-approved Long Form Consent Document may serve as the Written Summary.
- In addition to the individual authorized to obtain consent, there must be a witness present during the oral translation who is fluent in both English and the language of the Non-English Speaking Subject. If the individual authorized to obtain consent is not fluent in English and the language of the Non-English Speaking subject, an interpreter who is fluent in both languages is also required. The role of the witness is to attest to the accuracy of the translation and the apparent understanding of the subject.
- The Short Form Consent Document must be signed by the Non-English Speaking Subject and the witness. The Written Summary must be signed by the witness and the individual authorized to obtain consent. The name of the person who served as the interpreter should be noted in the research record as part of the documentation of the consent process.
- A copy of the Written Summary and the Short Form Consent Document must be given to the Non-English Speaking Subject. The original Written Summary and Short Form Consent Document should be kept in the subject's research record.
- When non-English speaking subjects were not anticipated and oral consent in any one language has been obtained from a significant number of subjects enrolled in a study, and enrollment is ongoing, the PI is expected to submit a protocol modification through Rascal to provide specific information (i.e., the number of subjects enrolled and their native language) to the IRB. A translated Long Form Consent Document with a certificate of translation must also be submitted and approved by the IRB prior to any additional Non-English Speaking Subjects who speak that particular language being enrolled in the study. A significant number is generally defined as 5% of the enrolled subjects. For studies with a total anticipated sample size of less than 40, the IRB will generally allow a maximum of two subjects to be enrolled using the short form process.

The following flow chart outlines the foregoing requirements:

Requirements for Translated Consent Document



* Generally defined as 5% of the enrolled subjects.

** For studies with a total anticipated sample size of less than 40, the IRB will generally allow a maximum of two subjects to be enrolled using the short form process.

Translations

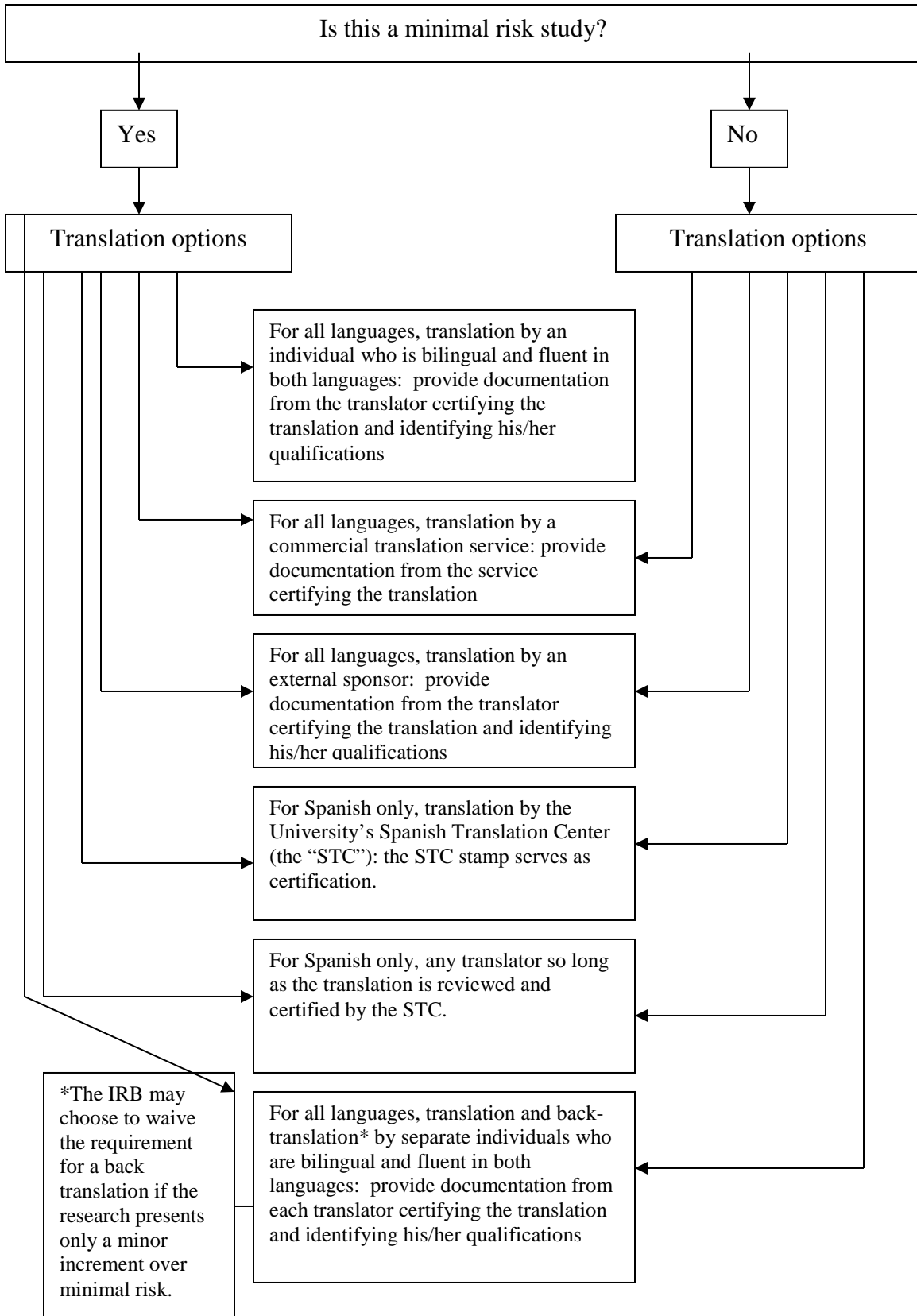
The IRB requires that all translations be certified by a translator who is acceptable to the IRB. The IRB does not itself certify translations. However, it maintains a list of acceptable translators; if a translator is on the list, he/she/it is deemed to be acceptable.

Acceptable translators include the following, although all may not be appropriate for all types of research:

- A commercial entity that provides translations as a service to the public.
- An individual who is bilingual and fluent in both English and the language of the Non-English Speaking Subject, for minimal risk studies.
- For research that is greater than minimal risk, the translated document must be back-translated into English by another individual who is also bilingual and fluent in both languages; for Spanish translations, the University's Spanish Translation Center (the **STC**) may be utilized in lieu of the back translation.
- If the research is a minor increment over minimal risk, the IRB may waive the requirement of the back translation into English.
- An external sponsor such as NIH or NSF or private industry.
- For Spanish translations, the STC; the STC stamp serves as an acceptable certification.
- For Spanish translations, any translator so long as the translation is reviewed and certified by the STC.

The following flow chart outlines the requirements for translators and certifications:

Acceptable Translators and Certifications



Effective Communication

When Non-English Speaking Subjects are being asked to participate in a study, investigators must ensure that there is adequate communication between the research team and such subjects in order for consent to be legally effective.

Unless the PI or a member of the research team is fluent in the prospective Non-English Speaking Subject's language, an interpreter will be necessary to facilitate the conversation during the consent process and communication throughout the course of the study. Interpreters should be fluent in English as well as in the language of the Non-English Speaking Subject.

Recruitment materials such as flyers, questionnaires, study calendars, instruction sheets, etc. must be translated in order to accommodate expected Non-English Speaking Subjects (i.e., a significant number of subjects who are not fluent in English). All translations of recruitment materials must be certified by an acceptable translator and approved by the IRB prior to their use.

<http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc>

In addition to informed consent forms, the STC is expert in translating Spanish-language brochures and research questionnaires to be used in studies. Information about the STC can be found on the CTO website at https://cto.cumc.columbia.edu/for_investigators.html.

2. Vulnerable Populations

Vulnerable populations include children, pregnant women, prisoners, handicapped or mentally disabled persons, persons with acute or severe physical or mental illness, persons who are economically or educationally disadvantaged, or persons who are vulnerable because they are institutionalized. If you believe that your study may include a vulnerable population, the IRB staff can assist you in understanding any additional requirements.

Prior to initial approval of a protocol, and at each continuing review, the IRB will determine that there are appropriate additional safeguards included in the study to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence.

To this end, the IRB may require that an advocate be provided, or that a legally authorized representative or health care proxy provide permission for enrollment, in addition to consent or assent from the subject, when the capacity of the prospective subject to provide legally effective consent is in question. Procedures for determining capacity must be described by the investigators when individuals who may lack capacity to consent will be considered for enrollment.

In any situation, but particularly when a prospective subject is considered to be vulnerable, the IRB may observe the consent process or require changes in recruitment procedures to eliminate or reduce elements of coercion or undue influence.

(<http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>)

Children

Children are a vulnerable research population and, as such, require additional protections when they are potential research subjects. At the same time, children should not be denied the benefits of participating in research. Federal regulations require that additional precautions be taken depending on the degree of risk involved in the research. In addition, the regulations also set forth requirements for obtaining parental/guardian permission and, where appropriate, assent by the children themselves. NIH policy has similar requirements.

<http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

The University has a [Policy on Research Involving Children](#) that includes a detailed explanation of the Policy and procedures.

The regulations relating to research involving children are governed by [Subpart D of 45 CFR 46](#) and [21 CFR 50](#) (collectively, **Subpart D**) and apply to all non-exempt research involving children conducted at Columbia or by Columbia researchers. See <http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm119111.htm>.

Please refer to the following terms defined in **Annex B** as they are important to understanding the Subpart D regulations:

- **Assent**
- **Child**
- **Guardian**
- **Parent**
- **Permission**
- **Section 404 Research**
- **Section 405 Research**
- **Section 406 Research**
- **Section 407 Research**
- **Ward**

The Subpart D regulations are highly technical but can be analyzed in three steps: (a) risk benefit analysis, (b) permission of the parent or guardian and (c) assent of the child.

Risk Benefit Analysis

In considering the risks of a study involving children, the investigator should note the following:

- Minimal risk should be considered in relation to the normal experiences of average, healthy, normal children.

- The potential harm or discomfort anticipated in research should be considered in relation to the harm or discomfort that average, healthy, normal children may encounter in their daily lives or experience in routine physical or psychological examinations or tests.
- The risk of harm or discomfort should be considered in relation to the ages of the children to be studied.
- The duration, as well as the probability and magnitude, of potential harm or discomfort should be considered.

Parental Permission

Subpart D requires that adequate provisions be made for soliciting the permission of the parents or guardian of each child involved in a research study. All of the requirements concerning informed consent apply to obtaining parental permission and the appropriate elements of consent must be included in a written informed consent document (i.e., a consent form that could apply to both adult participants in the study and parents of children in the study or a separate Parental Permission Form), unless otherwise waived by the IRB.

The IRB may waive the requirement for obtaining parental permission. See Section D.2 of the [Policy on Research Involving Children](#). If the IRB has not waived the requirement of parental permission, obtaining permission of only **one** parent is acceptable for Section 404 Research or Section 405 Research unless the IRB determines that permission from both parents is warranted.

If the IRB has not waived the requirement of parental permission, the permission of both parents must be obtained for Section 406 Research or Section 407 Research unless:

- One parent is deceased, unknown or lacks capacity to provide permission;
- One parent is not reasonably available; or
- One parent has legal responsibility for the care and custody of the child.

The investigator should document in the research record the efforts made to obtain permission from both parents unless not required to do so by the IRB.

If a person other than a parent signs a Parental Permission Form, the PI should, if possible, obtain documentary evidence that such person has been legally appointed as a guardian or, in the case of wards or foster children, that a state agency has legal custody or guardianship of the child. If such documentation is not available, the PI should call the IRB for assistance. A foster parent is not ordinarily authorized to provide parental or guardian permission.

Assent

Subpart D requires that adequate provisions be made for soliciting the assent of all children involved in research, when the children are capable of providing assent. In determining whether children are capable of assenting, the ages, maturity and psychological state of the children should be taken into account.

Please note that mere failure of the child to object should not, absent affirmative agreement, be construed as assent.

Assent is required for all non-exempt research involving children aged 7 years or more unless the IRB determines that:

- The capability of the child is so limited that he/she cannot reasonably be consulted;
- The research holds out the prospect of a direct benefit that is only available through participation in the research (i.e., research that offers a therapeutic benefit); or
- All of the following factors are present and the IRB has specifically waived the requirement to obtain assent:
 - The research involves no more than minimal risk;
 - The waiver will not adversely affect the rights and welfare of the subjects;
 - The research could not practically be carried out without the waiver; and
 - If appropriate, the subjects will be provided with additional pertinent information.

In general, children should be given developmentally appropriate information about a research study in language that is understandable to them, given their age, maturity and previous experiences. This information may be provided verbally. However, the provision of information is a matter of judgment for the investigator and the child's parents or guardian and there may be circumstances where information should not be given to a child. The IRB can provide assistance in this determination.

If assent is required, the process for obtaining assent, the content of the information provided and the format of the assent document, if any, depends on the age of the child.

- **Children aged 7-11 years:** If assent is not waived by the IRB, except as otherwise provided above, children in this age group should be fully informed about the research, using language appropriate to their age and maturity, and assent should be obtained from those deemed capable of making a meaningful decision. Assent should be solicited in the presence of a parent or guardian and the Parental Permission Form should include an acknowledgement by the investigator and the parent or guardian that verbal assent was obtained. If assent is not solicited, the reason for not soliciting assent should be noted in the research record for the subject.
- **Children ages 11-17:** If assent is not waived by the IRB, except as otherwise provided above, children in this age group should be fully informed about the

research and documented assent should be obtained. The child may either sign his/her own Assent Form or may co-sign the Parental Permission Form, so long as in either case, the Form is written in age appropriate language. If documented assent is not obtained, the reason for not obtaining assent should be noted in the research record for the subject.

In any research study that involves continuing diagnostic or therapeutic procedures, or any other form of research intervention (e.g., surveys) over time, attention should be paid to revising the information and assent documentation as the age of a child changes. In any case, any child who turns 18 during the course of a study must provide informed consent before his/her participation in the study continues.

Wards

Children who are wards may be included in Section 404 Research or Section 405 Research.

Children who are wards may be included in Section 406 Research or Section 407 Research only if such research is:

- related to their status as wards; or
- conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards.

If wards are to be included in any research study, the investigator must provide the IRB with detailed information about the proposed informed consent process as well as identity and authority of the individuals who will provide consent.

If wards are to be included in Section 406 Research or Section 407 Research, an advocate for each ward must be appointed in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate should be an individual who has the background and experience to act in the best interest of the child for the duration of the child's participation in the study and who is not associated in any other way with the research, the investigator or the ward's guardian organization.

In New York City, if wards are to be included in Section 406 Research or Section 407 Research, the Administration for Children's Services (**ACS**) must be notified and agree to the inclusion of wards in the study. In addition, permission for the enrollment of each ward in the study must be obtained from the person designated by the ACS to give such permission.

If a research study is to be conducted outside of New York City, the investigator should check appropriate state or local laws and regulations before conducting research to determine whether there are similar regulatory requirements and, if so, contact the appropriate governmental agency. The IRB can provide assistance in this determination.

Pregnant Women, Fetuses and Neonates

Pregnant women, fetuses and neonates (i.e., newborns) constitute vulnerable populations and, as such, require additional protection when they are research subjects. The regulations relating to this research can be found at [45 CFR 46, Subpart B](#). Distinction must be made between studies for which the reproduction status of the pregnant woman or the unique characteristics of fetuses and neonates are criteria for inclusion in the research, and studies for which the pregnancy status of the woman is incidental. Subpart B requirements are not applicable to the latter situation.

For additional details on the conditions that are applicable to (a) research involving pregnant women and fetuses, please see [45 CFR 46.204](#) and (b) research involving neonates, please see [45 CFR 46.205](#).

Columbia has developed guidance for obtaining consent from women during labor, in acknowledgement of the fact that some research can only be done during this period, it may not be possible in some circumstances to obtain consent before labor begins, and women who are capable of providing consent during labor and wish to participate in research should be able to do so. These guidelines are available from the HRPO.

Proposed informed consent procedures for pregnant women who are not in labor will be reviewed in consideration of the general requirements for informed consent, with special attention to the explanation of potential risks and benefits to both the woman and fetus. <http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>

Prisoners

Prisoners are a vulnerable population due to the fact that because of their incarceration, they may be under constraints that could affect their ability to make a truly voluntary and non-coerced decision whether or not to participate as subjects in research. The regulations relating to this research can be found at [45 CFR 46, Subpart C](#).

A prisoner is any individual involuntarily confined or detained in a penal institution. This includes individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by procedures which provide alternatives to incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

Please see [45 CFR 46, Subpart C](#) for details on the conditions that apply to research involving prisoners ([45 CFR 46.305](#)), including what types of research may be conducted with prisoners ([45 CFR 46.306](#)).

Please note that the definition of “minimal risk” for research with prisoners is different than for research not involving prisoners, in that the risk is relative to that encountered in

the daily lives of healthy individuals. In Subpart C, minimal risk is: the probability and magnitude of physical harm that is normally encountered in the daily lives, or in the routine medical, dental or psychological examination of healthy persons.

Students

Because the element of coercion or influence may be present in any use of students in research projects conducted by faculty, instructional staff or other researchers, any protocol including students as research subjects should justify the use of this population and identify how elements of coercion or undue influence will be addressed.

3. Same Day Elective Surgery or Procedure

When possible, the IRB aims to avoid seeking consent for research on the same day that an elective surgery or procedure is scheduled. However, for some research conducted on the same day as an elective procedure, researchers cannot prospectively identify and contact potential research subjects. In such instance, restricting research subjects to those who can be prospectively identified and contacted may render the research impracticable or would introduce bias into the subject pool.

Minimal Risk Research

For minimal risk research, seeking same day consent is allowable following appropriate IRB review, if the research may not otherwise be practicably conducted.

For protocols that meet the criteria for expedited review, such review may be conducted by the IRB Chair.

Research Posing a Minor Increment above Minimal Risk

For research posing a minor increment above minimal risk, seeking consent on the day of an elective surgery or procedure may be approved on a case by case basis by the convened IRB, through full Board review. The following criteria are considered when reviewing such requests:

- The research poses only a minor increment above minimal risk.
- The IRB protocol application must explicitly request permission to obtain same-day consent, and must describe the proposed consent process, including who will seek consent, and how this process will fit in with the schedule of clinical care.
- Same-day consent must be found by the IRB to be necessary to the research and to not place undue pressure on individuals to participate.
- The consent process must begin with a specific statement about the same day of procedure approach, and include a clear opportunity to decline participation (e.g., “We understand that some people will not want to discuss clinical research while

they are waiting for a procedure. If you do not want to discuss this research study, you do not need to do so.”).

- The patient/potential subject will be encouraged to invite an accompanying relative or friend to participate in discussions of research options.
- All potential subjects must be offered sufficient time to review the consent form and consider research participation before being asked for their decision.
- Whenever possible, an IRB approved information sheet should be mailed to potential research subjects prior to the procedure date containing the following information: (a) that the patient may be approached to consider research participation, (b) a description of the difference between research and standard practice and (c) a description of the voluntary nature of research participation.
- Consent must never be sought when a potential subject has received medications that may alter his/her cognitive state. Discussion should take place while the patient is still in possession of glasses, hearing aids or other necessary devices.
- Documentation in the research record must include the time at which the consent process started and the time at which consent was obtained.

Research that is Greater than Minimal Risk

The IRB will consider proposals for same day consent for research protocols that involve greater than a minor increment above minimal risk on a case by case basis. In general, such protocols will not be allowed to obtain informed consent on the same day of the elective procedure. However, there may be some research protocols that may provide potential therapeutic benefit and for which seeking consent prior to the day of the procedure may not be feasible. At a minimum, all of the above protections will need to be considered.

See [Columbia University Institutional Review Board Policy: Seeking Consent for Research Participation on the Day of an Elective Surgery or Procedure.](#)

G. Other Consents

1. HIPAA

The HIPAA Rules pertain to all clinical research studies that utilize identifiable PHI. The HIPAA Rules are codified at [45 CFR 160](#) and [45 CFR 164, Subparts A and E](#) and can be found at the HIPAA website of the OCR at <http://www.hhs.gov/ocr/hipaa>.

A helpful booklet, “*Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule,*” as well as companion pieces for clinical health records and health services research, published by HHS can be found at <http://privacyruleandresearch.nih.gov>.

The HIPAA Rules address the use and disclosure of PHI by Covered Entities or by workforce members of a Covered Entity. As CUMC is a Covered Entity, all CUMC investigators must comply with the HIPAA Rules in any study, including studies that are not “human subjects research”, exempt studies and research with biological materials and tissues. The HIPAA Rules also govern disclosure of data to individuals, whether affiliated with the Covered Entity or not, who propose to use such data for research purposes. Research involving only de-identified data is not subject to the HIPAA Rules.

Columbia’s HIPAA Policy and related procedures can be found at http://www.columbia.edu/cu/irb/documents/IRB_Privacy_Board_PolicyFINAL042808.pdf

The HIPAA Rules require that each Covered Entity have a Privacy Board to review protocols for HIPAA compliance. At Columbia, the IRB acts as the Privacy Board and is responsible for reviewing all HIPAA privacy requirements in each protocol submitted to the IRB.

Additional information may also be obtained via Rascal at <https://www.rascal.columbia.edu/comply/hipaa.html> or from the website maintained by the Privacy Office: <http://cumc.columbia.edu/hs/hipaa/policies/hipaa.html>.

Protected Health Information (PHI)

The HIPAA Rules define PHI as information that is created or received by a Covered Entity that relates to the past, present or future physical or mental health or condition of a patient, the provision of health care to a patient, or the past, present or future payment for the provision of health care to a patient, and that identifies the patient or for which there is a reasonable basis to believe that the information can be used to identify the patient. The HIPAA Rules list the following 18 identifiers (**HIPAA Identifiers**) that, if present, are considered to be sufficient information to identify an individual:

- Name
- All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geographical codes
- All elements of dates relating to the individual except year
- Telephone numbers
- Fax numbers
- Email addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers

- Device identifiers
- URLs
- IP addresses
- Biometric identifiers, including fingerprints and voiceprints
- Full face photos
- Any other unique identifying number, characteristic or code.

“Use” of PHI occurs within a Covered Entity and under the direct control of a Covered Entity. “Disclosure” of PHI occurs when PHI is provided to an individual who is not a workforce member of the Covered Entity or an entity that is not part of the Covered Entity. Workforce members include physicians, employees, volunteers, students, temporary staff and other members of the workforce with access to PHI.

More information on the HIPAA regulations can be found at <https://www.hhs.gov/hipaa/index.html>.

Criteria for IRB Approval

Columbia’s [HIPAA Policy](#) requires that use or disclosure of PHI for research must meet one of the following criteria to be approved by the IRB. The Policy sets forth procedures for each criterion and requires the review and approval of certain forms.

- A HIPAA authorization form will be signed by the study participant (Form A);
- A HIPAA waiver of authorization will be obtained from the IRB (Forms B and C);
- The activity qualifies as preparatory for research (Form D);
- The information used is solely on decedents (Form E);
- The information is compiled into a “limited data set” and a Data Use Agreement is signed (Form F); or
- The information is completely de-identified (Form G).

The required forms relating to each of the relevant criteria should be attached to each protocol. The forms are available in Rascal at <https://www.rascal.columbia.edu/servlet/edu.columbia.rascal.presentation.hipaa.servlets.HipaaMainServlet>. The protocol title and IRB number are automatically populated when the HIPAA form is attached to the protocol. The forms must be created in Rascal and attached to the protocol.

Use and Disclosure of PHI

Which HIPAA forms(s) to use is determined by the research activity and the PHI that will be accessed, used and/or disclosed during the research.

Prior to Research Project

- **Review Preparatory to Research (Form D).** PHI may be needed to identify prospective study participants or for purposes of protocol development or evaluation of Columbia as a research site. When searching for likely candidates for a study, investigators and CRCs may wish to review documents such as clinical databases, medical records, appointment logs, procedure boards or other retrospective or prospective data sources. Activities preparatory to research include preparing a research protocol, developing a hypothesis, writing a grant application or identifying subjects. A HIPAA Form D should be completed for these activities.

The HRPO will approve the review of medical information by a Columbia employee or healthcare provider if the following conditions are met:

- Access to PHI is solely for the purpose of identifying research participants, developing a research protocol or clinical trial site evaluation;
- The requested information is necessary for the purpose; and
- No PHI will be removed from Columbia or NYP premises.

Submitting Form D in Rascal also meets the NYP data security policy requirements for CUMC research with data stored partially or wholly in NYP data systems.

- **Recruitment Waiver of Authorization (Form C).** This is a waiver to use PHI to identify and contact potential research subjects other than through a treating physician. In addition to meeting the requirements set forth under **Waiver of HIPAA Authorization** below, the investigator must answer the following question: why would it be impractical to rely on the University or on an University-affiliated clinician with whom the potential participant has a treatment relationship, to contact the potential participant on your behalf?

During Research Project

- **HIPAA Authorization Form (Form A).** In order to use PHI in most clinical research, the investigator must obtain separate written HIPAA authorization from the individual to whom the PHI applies, either separately or as part of the consent document. The authorization must include the following items:
 - The specific information that will be used;
 - The people or organizations who may use or disclose the information (i.e., the research team);
 - The people or organizations who will receive the information (i.e., the sponsor, CRO, central laboratories, IRB, FDA, etc.);
 - The purpose of the use or disclosure, which must be study specific;
 - The expiration date (i.e., 10 years after the conclusion of the study);
 - The right to refuse to sign the authorization; and

- The right to revoke the authorization.

If a subject withdraws from a study, he/she must specifically revoke his/her HIPAA authorization. However, even if the authorization is revoked, the investigator may still use PHI to inform the sponsor, and PHI already submitted to the sponsor need not be withdrawn.

The research team may request that the informed consent and HIPAA authorization form be combined in one document. When the informed consent form includes all of the elements of a HIPAA authorization and is approved by the IRB, a HIPAA Authorization Form A is not required

- **Waiver of HIPAA Authorization (Form B).** In certain circumstances, generally when retrospective chart reviews or other medical records will be reviewed, but potential recruits will not be contacted, the IRB may waive the requirement that an investigator obtain HIPAA authorization from a study participant. The criteria required for a waiver are:
 - The use or disclosure involves no more than minimal risk to the individual based on the following:
 - There is an adequate plan to protect the PHI from improper use or disclosure;
 - There is an adequate plan to destroy the PHI as soon as practicable; and
 - There is adequate written assurance that the PHI will not be reused or re-disclosed to any other person or entity;
 - The research could not practicably be conducted without access to the PHI; and
 - The research could not practically be done without the waiver.
- **Research with Decedent’s Information (Form E).** A decedent’s PHI is subject to the Privacy Rule, and an investigator who seeks to use such information must:
 - Make certain representations of need for the information;
 - Describe the nature and the scope of the deceased patients’ information to which access is sought;
 - Verify that access to the requested information is solely for the purpose of research; and
 - The requested information is necessary for the research purpose.
- **Limited Data Set Pursuant to Data Use Agreement (Form F).** When an investigator proposes to conduct research using medical information at Columbia, the IRB will consider whether use of a “limited data set” is sufficient for the research purposes. A **Limited Data Set** is comprised of PHI that excludes all HIPAA Identifiers other than (a) dates such as admission, discharge, service, birth and death dates, (b) geographic information such as city, state, five digit or more zip code and (c) ages in years, months or days or hours.

To use a Limited Data Set, an investigator must sign a Data Use Agreement that limits who can use or receive the Limited Data Set, requires the investigator to agree not to re-identify the data to contact the individuals, and contains adequate

assurance that appropriate safeguards will be used to prevent improper use or disclosure of the Limited Data Set. A Data Use Agreement form is available in the Rascal HIPAA module as Form F. Data Use Agreements received from other institutions must be attached to the research protocol and reviewed by the IRB.

- **Research with De-Identified Data (Form G).** To use fully de-identified data, the investigator should create a HIPAA Form G, which is an attestation that the data collected and used for research purposes will not include any of the HIPAA Identifiers.

Accounting of Disclosures

Subjects have a right to receive an accounting of disclosures of their PHI and, as a result, CRCs must record all applicable disclosures except (a) pursuant to a HIPAA authorization or (b) when data is disclosed to a Business Associate (i.e., an entity that has contracted with Columbia to assist in business processes of health care or clinical research). The accounting must include:

- Date of disclosure;
- Name of subject and name and address of person/entity to whom the PHI was disclosed;
- Brief description of the information disclosed; and
- Brief explanation of the reason for the disclosure.

2. Genetic Research

Section 79-L of the New York State Civil Rights Law (**Section 79-L**) <http://public.leginfo.state.ny.us/lawssrch.cgi?NVLWO:>) was enacted in 1996 to provide asymptomatic individuals who are considering whether to have predispositional genetic testing sufficient information to assess the benefits and consequences of such testing. Unlike diagnostic genetic tests that confirm the presence or absence of a disease, predispositional genetic tests cannot predict with certainty the risk of developing a disease. Section 79-L provides that a genetic test may not be performed on any biological sample taken from an individual without his/her prior written informed consent that meets certain strict disclosure standards. Under Section 79-L, a **Genetic Test** is defined **only** as a test conducted to learn whether an asymptomatic person or his/her offspring has a genetic predisposition to a disease or disorder.

The University has a Policy on [Research Involving Genetic Testing](#) under Section 79-L of the New York State Civil Rights Law (the **Genetic Testing Policy**) The following summarizes the consent requirements under Section 79-L for research using genetic testing on biological samples, which differ depending on the circumstances of the use. **Please note that these requirements cover ONLY genetic testing for research use and not for clinical use.**

- **Genetic Tests on biological samples intended to be used for specific research purposes.** Any Genetic Test on a biological sample of an individual that has been collected with the specific intent that the sample be used for genetic testing for research purposes requires (a) an IRB-approved protocol and (b) a written informed consent meeting the requirements of paragraph (b) of subdivision (2) of Section 79-L.
- **Genetic Tests on anonymous biological samples to be used for research.** Any Genetic Test on an anonymous biological sample to be used for research purposes does not require a written informed consent, but does require an IRB-approved protocol that ensures the anonymity of the source of the sample.
- **Genetic Tests on stored biological samples collected for general research purposes without consent for genetic testing.** Any Genetic Test on a biological sample of an individual who at the time that the sample was stored provided consent to use the sample for general research purposes, but did not provide specific written consent for the sample to be used for genetic testing requires (a) an IRB-approved protocol, (b) that the prior consent did not specify time limits or other factors that would restrict the use of the sample for genetic testing and (c) either (i) the sample has been permanently stripped of identifying information or (ii) an IRB-approved coding system has been established to protect the identity of the individual.
- **Genetic Tests on stored biological samples collected for general research purposes with consent for genetic testing.** Any Genetic Test on a biological sample of an individual who at the time the sample was stored provided consent to use the sample for general research purposes, including the use of the sample for genetic testing requires (a) an IRB-approved protocol and (b) a written informed consent meeting the requirements of paragraph (e) of subdivision (9) of Section 79-L, provided that the results of such testing may not be disclosed to the individual without the written informed consent of such individual meeting the requirements of paragraph (b) of subdivision (2) of Section 79-L.
- **Genetic Tests on stored biological samples collected without consent for general research purposes.** Any Genetic Test on a biological sample of an individual who provided consent to store the sample, but at the time the sample was stored did not provide specific written consent for the sample to be used either for general research purposes or genetic testing requires (a) an IRB-approved protocol and (b) a written informed consent meeting the requirements of paragraph (b) of subdivision (2) of Section 79-L.

It is a University policy that if the results of genetic testing will be provided to a research subject, the results must be confirmed by a CLIA or New York State certified laboratory prior to being released.

For Further information, see the Genetic Testing Policy.

CUMC requires a separate consent to be signed for **clinical** genetic testing. See the CUMC Genetic Testing Informed Consent Policy (http://www.cumc.columbia.edu/dept/irb/policies/ICF_Genetic_Text.htm).

3. HIV Research

It is PHS policy that when HIV testing is conducted or supported by PHS, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling. Individuals may not be given the option “not to know” the result, unless there are compelling and immediate reasons that justify not informing a particular individual that he/she is sero-positive (e.g., suicide risk) or the IRB has approved the exception based on certain specified criteria. The policy can be found at <http://www.hhs.gov/ohrp/policy/hcdc88jun.html>.

H. Reconsenting Subjects

When a protocol modification includes new information related to risks, additional or modified procedures, or other factors that may affect subjects’ willingness to continue participation, the IRB must consider options for providing this information to participants. These may include obtaining signatures on a revised consent form, providing an information sheet to participants, or verbally informing subjects by telephone or in person. Regardless of the method selected, content of the documents or scripts that will be used should be provided to the IRB for review, and means of documenting notification to the subjects should be specified. If there are changes to the consent form, the IRB may specify that subjects must sign the new form.

(<http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>)

X. WORKING WITH STUDY SUBJECTS: MANAGING THE STUDY

A. Introduction

In many clinical research studies, the CRC is the member of the research team most involved with the day to day management of the trial and is the primary point of contact with the study participants. As such, the CRC plays a crucial role in the successful outcome of the study. This chapter and the following chapter will describe the myriad of tasks that a CRC may be called upon to perform during the course of a trial.

B. Study Procedures

1. Types of Procedures

The study procedures for a clinical research project are outlined in the study's protocol, usually under the heading "Study Assessments" or "Schedule of Events." Depending on the type of trial, study procedures may include the following assessments:

- Physical exam
- Urine tests
- Blood tests
- Other clinical laboratory tests
- Vital signs
- Adverse event assessment
- Concomitant medication review
- Surgical procedures (e.g., biopsies, stent placement)
- Patient diary review
- Electrocardiogram (ECG or EKG)
- Imaging procedures (e.g., CT scans, MRIs)
- Neurological assessments
- Physical and mental health surveys

2. Scheduling

Once the procedures for a study are established, either by the sponsor or the PI, the CRC must set up a schedule of procedures for each study participant. Procedures should be scheduled well in advance. If possible, the CRC should schedule all study appointments at the research subject's first ("baseline") visit to enable the subject to make work and transportation arrangements. If the study will take place over a long period of time and scheduling all visits at the beginning of the trial is not feasible, the CRC should schedule the next several procedures that follow the baseline visit.

Scheduling subjects for study visits is more difficult than scheduling normal office visits because study visits must be in accordance with the protocol and there is not much flexibility around the required visit dates. Since it is not always possible for subjects to come in for a study visit on the exact date, most protocols allow a few days before or after the protocol date to provide a “visit window”.

Please note that each visit window is calculated by going back to the starting or baseline date, rather than from the previous visit so as not to add more days onto the study schedule. If the sponsor does not provide a reference sheet, it is useful to make one yourself. The following is an example:

Patient Number	Baseline (+/- 1day)	Week 1 Visit (+/- 1 day)	Week 2 Visit (+/- 1 day)	Week 4 Visit (+/- 1 day)
001	April 4 (Actual)	April 11 (April 10, 11,12)	April 18 (April 17,18,19)	May 2 (May 1,2,3)
002	April 8 (Actual)	April 15 (April 14,15,16)	April 22 (April 21,22,23)	May 6 (May 5,6,7)

If study subjects are scheduled in advance, it is important for the CRC to send postcard and telephone reminders before each scheduled visit. Coming in for scheduled visits is necessary for study compliance, data analysis and sponsor reimbursement.

3. Visit Tracking

Subject visits should be conducted in accordance with the Schedule of Events in the protocol and the Delegation of Authority Log.

It is important to document patient visits by developing a spreadsheet or data base that tracks the following information by subject name or ID Number:

- Dates of anticipated follow-up visits
- Dates of actual follow-up visits
- Comments.

4. Visits

As the CRC may be the primary contact with the subject, it is important that all of the information that is required by the protocol in a study visit be obtained, as well as a checklist of information needed and questions that should be asked. The following are examples:

- Has the patient had any side effects?
- Has the patient had any other medical problems?

- Has there been any interruption in study medications?
- Have there been changes in any medications being taken by the patient?
- Have all protocol requirements been observed?
- Has the patient used any test articles correctly?

In addition, during the visit the CRC may review the upcoming schedule of visits and provide the subjects with the necessary paperwork for procedures to be done.

5. Accessing Medical Records

CUMC and NYP provide access to several online patient information systems containing clinical and administrative data through the following web-based applications:

System	Type of Data
IDX	Diagnoses, procedures, past and future outpatient appointments (used for scheduling)
Eclipsys	Current census and comprehensive clinical information (including medications ordered and received and flowsheets)
iNYP	Lab results, radiology and pathology reports, EKGs, daily clinical notes, operative notes and discharge summaries
Crown	Outpatient documentation
Amicas	CT Scans, MRIs
Paper based medical records	All inpatient documentation not found online

IDX and Crown are CUMC systems; Eclipsys, iNYP and Amicas are NYP systems. Please contact your DA for information about how to get access to these systems.

To request authorization to access a patient’s medical records via electronic health information systems, a Systems Access form, found at the link below, must be completed, signed by a director, a department chair or a physician, and submitted to the Help Desk at Information Services. http://www.nyp.org/pdf/is_access_form.pdf.

As per the NYP Code of Conduct, CRCs must actively protect and safeguard patient information. CRCs may only access a patient’s chart or medical data when they are involved in that patient’s care, or when they need access to the chart because of research requirements. CRCs may not reveal information unless it is supported by a legitimate clinical or business purpose.

See also **Working with Study Subjects: Informed Consent: Other Consents - HIPAA (Chapter IX, Section G(1))** for a discussion of the HIPAA requirements with respect to the use or disclosure of medical information.

6. Handling and Shipping Biological Samples

One of the responsibilities of a CRC in a clinical research study may be to ship biological samples such as blood, urine or tissue to a central location for analysis. Prior to handling biological materials, CRCs must take a Bloodborne Pathogens/Infection Control Training course in Rascal. See **Getting Started: Training: Mandatory Training – Environmental Health and Safety (Chapter III, Section C(6))** for further details on the course. If a laboratory handbook is provided by the sponsor, CRCs should follow the sample processing instructions in such handbook.

CRCs must also complete the Shipping Biological Materials Training course in Rascal. See **Getting Started: Training: Mandatory Training – Environmental Health and Safety (Chapter III, Section C(6))** for further details on the course. Since some biological materials are classified as dangerous goods or hazardous materials, anyone shipping such materials to another institution must comply with federal Department of Transportation regulations, including those on training, certification, packaging, labeling and documentation (<http://ehs.columbia.edu/ShippingBiological.html>). Inter-campus transport within the University is also subject to specific conditions and restrictions (<http://ehs.columbia.edu/Intercampus.html>).

CRCs should use shipping materials provided by the sponsor, as applicable, to protect the integrity of biological samples. The sponsor often provides the packaging for Biological Substance, Category B shipments that take place during the course of a clinical trial. If the material is reasonably expected to contain a pathogen or the study involves testing for an infectious disease, those individuals with shipping responsibilities must obtain from the sponsor documentation that the packing complies with regulations regarding labeling, packaging strength and containment ability. Such individual is also responsible for ensuring that the sponsor has provided properly marked and labeled packages and for compliance with all applicable shipping rules.

If dry ice is needed for shipping biological materials, it is either provided by the sponsor or can be obtained from local vendors. See **Getting Started: Training: Mandatory Training – Environmental Health and Safety (Chapter III, Section C(6))** for training requirements.

A CRC should keep track of specimens that have been sent out. An example of a Specimen Shipping Log can be found in **Annex F**. This Log is your insurance if there is a specimen damaged or lost.

C. Investigational Products

Responsibility for the use and accountability of investigational products in a research study rests with the PI, who may delegate some or all of his/her duties to an appropriate person.

1. Drugs

Research Pharmacy

At CUMC, the Research Pharmacy provides pharmacy services to support research both at CUMC and NYP. The Research Pharmacy is equipped to compound, package, dispense, blend, randomize and manage all dosage forms for all routes of administration. Additionally, the Research Pharmacy is able to handle drug ordering, inventory, accountability and return shipments for study drug products, including controlled substances.

You can email the research pharmacy at researchpharmacy@columbia.edu. More information about the CUMC Research Pharmacy can be found on the CTO website: <https://cto.cumc.columbia.edu/pharmacy/index.html> The use and control of investigational drugs at CUMC and NYP are governed by two Policies: one relating to inpatients: <http://cumc.columbia.edu/dept/irb/policies/documents/InvestigationalDrugsInpatient10.10finalDS.pdf> and the other relating to outpatients: <http://cumc.columbia.edu/dept/irb/policies/documents/InvestigationalDrugsOutpatient10.10finalDS.pdf>, as well as NYP Policy P168: Investigational Drugs: Use and Control of Investigational Drugs <http://inonet.nyp.org/QA/HospManual/MultipleLi/P168InvestigationalDrugs.pdf>. As stated in these policies, with very limited exceptions, you must use the Research Pharmacy to store and dispense all investigational drugs.

Investigational drug is defined in the Policies as

- Any drug not approved by the FDA that is being studied under an IND; and
- Any drug approved by the FDA that is central to the design of a research study and is being provided by the sponsor of the study or the investigator involved in the study.

If a study requires the services of the Research Pharmacy, the CRC should obtain a Research Pharmacy Cost Estimate Report Form from the CTO website (<https://cto.cumc.columbia.edu/pharmacy/docs/costestimaterquestform91812.pdf>) and complete it while the protocol is being drafted. A cost estimate will be generated by the Pharmacy. The CRC must supply the Research Pharmacy with all required study information and the protocol.

Any use of an investigational drug must be included in the study's protocol and be approved by the IRB. All protocols that include commercially available drugs supplied by NYP must be approved by the NYP Pharmacy Department.

All professionals involved in the storage, dispensing and administration of investigational drugs must hold active licenses in good standing with New York State and adhere to CUMC and NYP credentialing requirements. When Schedule II-IV Controlled Substances are used in a research study, all investigators who prescribe such controlled substances must obtain a "Class 4 Researcher" license issued by the New York State Department of Health (NYSDOH). When Schedule I Controlled Substances are used, investigators must obtain a Class 7 license from the NYSDOH and a special registration from the U.S. Drug Enforcement Administration. See also the [Columbia University Policy for the Acquisition, Use and Disposal of Controlled Substances in Research](#)

The use of an investigational drug at Columbia involves the following factors:

- **Storage.** All investigational drugs must be stored within the Research Pharmacy or an area controlled by the Research Pharmacy where investigational drug supplies are stored. Storage in the Research Pharmacy helps maintain blinding, where applicable, and provides continuous temperature monitoring
- **Inventory.** The Research Pharmacy will maintain an inventory of the investigational drugs, including the following:
 - Documenting the shipment upon its receipt
 - Storing each agent separately by protocol in a secure area with proper labeling
 - Providing continuous temperature monitoring to maintain proper storage conditions
 - Maintaining separate records for each agent by strength, dosage form and protocol
 - Maintaining current inventory
 - Ordering additional quantities as required, for timely dispensation
 - Verifying medication reconciliation of study drugs returned by the patient
 - Providing proper destruction or its return to the manufacturer (or distributor)
- **Accountability.** The Research Pharmacy will also maintain an accountability log to accurately document transactions of an investigational agent. There are four general transactions that will be recorded on an accountability log:
 - **Receipt** from the manufacturer (or distributor)
 - **Dispensing** to a patient
 - **Destruction or Return** to the manufacturer (or distributor)
 - **Transfer** to another site
- **Ordering.** Only the PI or a co-investigator may write an order for an investigational drug. Prior to dispensing any drug, a complete medication order

must be written, signed and made available in the patient's medical record and NYP's medication profiling system.

Note: Each order of an investigational drug must be written and signed by the appropriate physician at the time that the order is submitted; copies of previously written and signed orders may never be used for new orders.

- **Dispensing.** All investigational drugs must be dispensed either directly by the Research Pharmacy or from a Research Pharmacy-controlled automated dispensing cabinet. All dispensing procedures must be approved by the Research Pharmacy before study initiation.

The following information must be made available for review by any clinician or medical personnel involved in the care of the subject prior to the administration of an investigational drug to an inpatient:

- Name of study protocol and protocol number assigned by the IRB;
 - Name of the investigational drug and any synonyms;
 - PI and co-investigator(s);
 - Preparations (dosage form and strength) available from the Research Pharmacy;
 - All pertinent data concerning the storage and preparation of the investigational drug (if the item is to be reconstituted, the specific diluents and procedure for dilution must be included and the subsequent stability of the reconstituted solution must be stated);
 - Dilution and compatibility data (e.g., intravenous fluid compatibility) applicable to parenteral or any extemporaneous preparations;
 - Method of administration;
 - Any special information related to administration;
 - Expected therapeutic effect and potential adverse effects (specific information related to monitoring first dose response and longer term effects should be included); and
 - Any other important information relevant to the product.
- **Labeling.** The proper labeling of prescription medication is required by federal and state law as well as GCP Guidelines. See [Investigational Drugs – Inpatient](#) and [Investigational Drugs - Outpatient](#) under “Selected University Research Policies and Guidances – CU Research Pharmacy Policies” on the CUMC IRB Website for the information that must be included on the labels for inpatient drugs and outpatient drugs.

In some clinical studies, the sponsor may provide investigational agents in pre-packaged containers; however, the subject specific labeling is still placed on these containers to supplement the missing information. Supplemental tear-off labels may also be present on pre-packaged study drug containers, which are usually forwarded to the CRC for placement on the patient's CRF as part of the procedures for tracking and maintaining accountability for an investigational agent.

Some supplemental tear-off labels may contain un-blinding information, only to be accessed when the investigator deems it clinically necessary to un-blind the patient's treatment. Each protocol has specific procedures for un-blinding a patient and these un-blinding labels are usually kept in the Research Pharmacy or another secure location.

- **Administration.** Any investigational drug may be administered to a patient only by a physician, a nurse practitioner or a registered nurse.
- **Randomization.** Randomization to determine a patient's treatment assignment will occur prior to any dispensation of the study drug from the Research Pharmacy. The actual document (e.g., fax, email or list) that links the patient identification and/or randomization number to a specific treatment assignment also serves as a source document to track and maintain accountability for an investigational agent.
- **Blinding.** Depending on the design of the study, the Research Pharmacy may need to take steps during the preparation and/or dispensation process to maintain the blind for everyone else. Such steps may not only include labeling the agent in a blinded fashion but, for example, covering the container so the solution is masked and indistinguishable or making sure the time spent preparing the placebo is the same as when preparing the active treatment.
- **Disposal.** All unused or expired investigational drugs must be returned to the Research Pharmacy. Drugs are subsequently either returned to the sponsor or supplier or EH&S manages their disposal or destruction.

2. Devices

At CUMC, investigational devices are not handled by the Research Pharmacy. Instead, the ordering, accountability, handling and storage of devices is the responsibility of the PI and procedures should be determined prior to submission of a protocol to the IRB.

The IRB considers the following elements when reviewing a protocol for any study using a non-FDA approved device:

- When ordering of devices will begin;
- How and by whom the devices will be ordered;
- Who will receive the devices;
- How device accountability will be documented, including receipt from the manufacturer, method for labeling and tracking individual devices, date of use, subject identifier and lot number of the device, and return of (or destruction of in accordance with manufacturer's instructions/protocol) unused devices to the manufacturer or sponsor;
- Who may handle the devices;
- Who will ensure the sterility of the device prior to use;

- In what manner will devices be stored to ensure accountability, sterility and integrity of packing;
- What are the procedures for disposing of the devices; and
- If the device will be explanted from the subject, plans to first send the device to the Department of Pathology for their review in accordance with standard practice.

The IRB has the statutory authority to determine whether a device is a Significant Risk Device. See **The ABC's of FDA Research: Sponsor-Investigator Research – Summary of IDE Process (Chapter II, Section E(4))** for further information.

Certain devices may not be used prior to obtaining NGS or CMS approval if Medicare is to be billed for the device. See **Preparing for a Study: Review and Finalization of Proposals and Contracts: Approval Process – Additional Approvals and Certifications (Chapter VI, Section D(2))** and **Initiating a Study: NYP – Billing (Chapter VII, Section C(1))** for further information.

The CRC is responsible for maintaining the accountability log for devices. An example of a Device Accountability Log can be found in **Annex F**.

There are special procedures for ordering and receiving devices that have been agreed to by CUMC and NYP that are described in **Initiating a Study: NYP – Billing (Chapter VII, Section C(1))**.

D. Subject Reimbursement/Compensation

Clinical research often relies on volunteers to participate in studies. It is not uncommon for a researcher to reimburse subjects for travel or other expenses that they may incur as a result of participation in a study. Some studies may also offer compensation as a means to attract volunteers.

The IRB reviews all proposed plans for reimbursement or compensation provided to subjects to ensure that such payments are not coercive or unduly influential. Another consideration of the IRB, particularly for research involving the collection of sensitive data, is that the confidentiality of the subject is protected during the payment process if information about the subject must be forwarded outside the research team. The HRPO provides specially designed receipt books for this purpose.

For further information, see the University's [Petty Cash Policy](#) and the [CUMC Human Subjects Research Reimbursement/Compensation to Study Participants Policy](#).

1. Annual Payments of Less than \$600

Payments of less than \$600 per year to any subject are paid (a) by requisitioning a check for the payment, (b) out of a petty cash fund for the study or (c) by giving the patient a bank money card or parking passes. Use of a petty cash fund should be in accordance with the following procedures.

Establishing the Petty Cash Fund

To establish a petty cash fund, a CRC must send a check requisition with a letter of explanation signed by a member of the department that has appropriate signing authority to the General Accounting and Financial Reporting Department of the Office of the Controller (the **Petty Cash Office**). On the check requisition, the name of the custodian should be printed or typed in the “Payee” section. Also provide a financial account number and all other appropriate information (i.e., the department’s address, the custodian’s social security number, etc.). The letter of explanation should include:

- The reason for the fund;
- The dollar amount of the fund (base amount – see guidelines below);
- The name and title of the individual who will act as the fund custodian. The custodian may be any full-time salaried officer or staff employee approved by the department;
- A description of how and where the funds will be secured; and
- Approval by the appropriate departmental officer.

A petty cash fund number will be assigned by the Petty Cash Office to be used to increase, draw on or close the petty cash fund.

The fund initiator is required to justify the base amount of the fund, regardless of funding source, as determined by the following:

- Projected subject volume per week/month
- Projected reimbursement amount per subject
- Projected time lag for fund reimbursement

Preparing a Receipt

When cash is distributed to the subject, the CRC should prepare a receipt for the subject to sign. All receipts for human subjects need to be HIPAA compliant. A three ply receipt with the following fields is currently available to help comply with HIPAA:

- Requisition number
- Date
- Protocol name or number
- Checkbox for “subject reimbursement” or “subject compensation”
- Amount paid
- Name and signature of study coordinator
- Name of study subject*

- Signature of study subject*

* Under HIPAA guidelines, these items are considered PHI and will not be included on the third copy of the receipt, which is submitted to Accounts Payable.

The three copies of the receipts are distributed as follows:

- Copy 1 is to be given as a receipt to the subject.
- Copy 2 must be kept at the research site as part of the permanent confidential records.
- Copy 3 will be temporarily retained by the CRC until he/she seeks to replenish the petty cash fund. At that time, this copy will be submitted to Accounts Payable.

Individual receipt forms or booklets of forms are available at the HRPO locations at CUMC or on the Morningside campus.

Requesting Reimbursement From the Fund

The PI or designated CRC will periodically (weekly/monthly) batch and tally up the receipts and submit them to the fund custodian for reimbursement.

2. Annual Payments of \$600 or More

According to IRS regulations, payments to subjects of \$600 or more are considered to be taxable compensation to the subject and reportable to the IRS.

A series of payments or a single payment of \$600 or more should be made in accordance with the following procedures:

Series of Payments

If a *series* of subject payments results in total compensation of \$600 or more, the DA or CRC will:

- Prepare a W-9 Form providing the subject's name, address and social security number and submit it to the Controller's Office. A memorandum must accompany the W-9 Form providing the amount of compensation to the subject. The memo and W-9 Form must be mailed to: 615 W. 131st Street, 3rd Floor, Attn: AP Supervisor – 1099 Reporting.
- An IRS 1099 Form will be issued to the recipient.

Single Payment

If a *single* subject payment is greater than \$600, the DA or CRC will:

- Enter a check request through AP/CAR providing the amount of the check, as well as the name, address and social security number of the subject.
- Prepare a W-9 Form providing the subject's name, address and social security number and submit it to the Controller's Office. A memorandum must accompany the W-9 Form providing the amount of compensation to the subject. The memo and W-9 Form must be mailed to: 615 W. 131st Street, 3rd Floor, Attn: AP Supervisor – 1099 Reporting.
- An IRS 1099 Form will be issued to the recipient.

Informed Consent Requirements

The informed consent document, reinforced by the informed consent process, must clearly iterate the responsibility of the institution to report to the IRS as taxable income all payments to an individual subject aggregating \$600 or more in a calendar year. The consent form must reflect the specific information being reported to the IRS (i.e., subject name, social security number, address, amount of payment). The IRB must review and approve the informed consent document prior to implementation and as stipulated in the informed consent policy.

<http://www.cumc.columbia.edu/dept/irb/policies/documents/Compensation-ReimbursementPolicy.041205.Final.doc>

3. Subject Compensation for Injury

Typically, the sponsor of a clinical trial will agree that any costs relating to injuries to a subject in the course of a study will be paid by the sponsor.

Federal regulations require certain disclosures in an informed consent form for greater than minimal risk research with respect to subject reimbursement:

- For research involving more than minimal risk, an explanation as to whether any compensation will be paid and an explanation as to whether any medical treatments will be available if injury occurs and, if so, what they consist of or where further information may be obtained ([45 CFR 46.116\(a\)\(6\)](#) and [21 CFR 50.25\(a\)\(6\)](#)).
- 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 ([45 CFR 46.116\(a\)\(7\)](#) and [21 CFR 50.25\(a\)\(7\)](#)).

Consent forms for protocols that require research-related injury language would include either a standard Columbia University statement about coverage of research-related injury costs (available in Rascal's Consent Builder module and on the HRPO website) or a statement that is customized to the coverage provisions offered by the sponsor.

Following IRB approval, the CTO and SPA staff review the approved informed consent form to ensure that the injury protection information is consistent with the CTA.

E. Confidentiality and Privacy

There are many types of data that may be obtained for research purposes. A non-exclusive list includes information that may be collected via surveys, interviews, questionnaires, diaries, medical records, medical history, diagnostic procedures and analysis of tissues (e.g., blood tests, radiological scans and pathology reports), administration of treatments or therapies, etc. Additionally, data obtained for research purposes may be collected via different processes, such as paper forms, electronically, audio or visual recordings, etc. Research data includes both the actual information that is collected, as well as any notes or summaries that a researcher makes about human subjects. Furthermore, research data also includes information that was already collected by others and which will be used in a study that conducts secondary analysis of data.

Ensuring that there are adequate provisions to protect privacy of subjects and to maintain the confidentiality of data is mandated both by the IRB and by the following federal regulations: [45 CFR 46.111\(a\)\(7\)](#) and [21 CFR 56.111\(a\)\(7\)](#).

1. Data Security Plans

Every research study that involves potential risk to human subjects must include a data security plan.

At the time of initial review, the IRB ensures that each protocol includes provisions for protecting the privacy of subjects and maintaining the confidentiality of study data. The IRB considers privacy and confidentiality protections that will be in place during recruitment (i.e., by review of the recruitment plan), enrollment (i.e., by considering whether the subject being seen by others in association with the researcher could result in harm to the subject) and participation (i.e., by examining the extent of electronic security measures to be used to protect data).

The methods or processes for protecting the confidentiality of research should be proportionate to the level of potential risk to subjects if the data is compromised. The University considers data constituting PHI to be the most sensitive data and therefore require the most stringent protections.

For purposes of the IRB's Policy: [Data Security Plans Involving the Use, Storage or Transmission of Electronic Research Data Constituting Sensitive Data](#), **Sensitive Data** is defined as any information protected by federal, state and local laws and regulations or industry standards, such as HIPAA, the Health Information Technology for Economic Clinical Health Act (HITECH), the U.S. Family Educational Rights and Privacy Act (FERPA), the New York State Information Security Breach and Notification Act, the

New York State HIV Testing Law, similar state laws and the Payment Card Industry Data Security Standard (PCI-DSS). Included in Sensitive Data are PHI and PII.

PHI is defined in the [Columbia University Information Security Charter](#) (the **Charter**) for purposes of the University's data security policies as any information processed, transmitted or stored by a Covered Entity that relates to the past, present or future physical or mental health or condition of an individual, the provision of health care to an individual or the past, present or future payment for health care and (a) identifies the individual or (b) with respect to which there is a reasonable basis to believe that the information can be used to identify the individual.

PII is defined as any information about an individual that (a) can be used to distinguish or trace an individual's identity, such as name, date and place of birth, mother's maiden name and biometric records, (b) is linked or linkable to an individual, such as medical, educational, financial and employment information, which if lost, compromised or disclosed without authorization, could result in harm to that individual and (c) is protected by federal, state and local laws and regulations or industry standards.

Data Storage

The following methods of storing electronic research data containing Sensitive Data are acceptable to the IRB:

- The data is stored on a System (as defined in the Charter) in compliance with the [Columbia University Registration and Protection of Systems Policy](#) (the **Systems Policy**). The specific server name and IP address and, if applicable and provided to the user, a copy of the CUMC Information Technology System Certification Certificate should be included with the protocol.
- If the data is stored on an Endpoint (as defined in the Charter) in compliance with the [Columbia University Registration and Protection of Endpoints Policy](#) (the **Endpoints Policy**). The inclusion of a statement to such effect in a protocol will constitute a certification by the PI that each endpoint to be used in the study will be so protected.

Data Transmission

An acceptable data security plan must provide that all electronic transmissions of Sensitive Data over the internet (including by email), file transfers or other data transfer modalities, are made in compliance with the Systems Policy or the Endpoints Policy and the [Columbia University Email Usage Policy](#).

CRCs must ensure that that subjects' privacy is protected and the confidentiality of data is maintained by adhering to privacy and confidentiality protections during subject recruitment, enrollment and participation in the study. Paper records should be stored

securely and electronic data should be protected from unauthorized access. For electronic medical records, CRCs must maintain computer workstations and access codes in a confidential and responsible manner. CRCs may not share computer identification information and passwords. In addition, CRCs may not discuss patient information in any public area, including elevators, hallways and dining areas.

See **Working with Study Subjects: Informed Consent: Other Consents - HIPAA (Chapter IX, Section G(1))** for a discussion of HIPAA requirements.

2. Certificates of Confidentiality

At times, research may involve the collection of data that, if disclosed, could have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. In these cases, the IRB may require that a Certificate of Confidentiality (COC) be obtained.

COCs are issued by the NIH to protect identifiable research information from forced disclosures in any civil, criminal, administrative, legislative or other proceeding. Information on COCs is available on the NIH website at the COC Kiosk. The Kiosk includes background information on COCs, application instructions, FAQs, information on communicable disease reporting policy and a list of contacts. See <https://humansubjects.nih.gov/coc/index>

3. HITECH

The Health Information Technology for Economic and Clinical Health Act (**HITECH**), part of the American Recovery and Reinvestment Act of 2009 (**ARRA**), established notification requirements to report the loss or theft of Sensitive Data. These requirements apply in both the clinical and research contexts. Examples of such security breaches include compromise of unprotected PHI through:

- Lost or stolen laptops, USB drives, CD/DVD/Zip drives, etc. with stored data
- A compromised account that is used to look up data (e.g., unauthorized user has had access to the account)
- A compromised workstation or server that contains data
- Accidental disclosure of data to unauthorized recipients (e.g., sending data to an incorrect email address).

Any loss of, or breach of security relating to, Sensitive Data used in research must be reported (a) to the IRB in Rascal as a Unanticipated Problem Involving Risks to Subjects or Others and (b) in compliance with the [Columbia University Electronic Data Security Breach Reporting and Response Policy](#).

4. Social Security Numbers

The University is required by the New York Social Security Number Protection Law to protect the confidentiality of social security numbers (SSNs).

Generally, SSNs should not be collected unless permitted by the [Columbia University Social Security Number \(SSN\) Usage Policy](#) (the **SSN Policy**) or the IRB for research purposes. The IRB recognizes that the collection and use of SSNs is essential for the conduct of some research activities (e.g., epidemiological studies collecting mortality statistics). Any plans to collect SSNs for research purposes must be submitted to and approved by the IRB prior to such collection. The submission to the IRB must include a justification for the collection of SSNs and provide the following:

- An explanation of how and where the SSNs will be stored;
- Who will have access to the data; and
- The plan to protect the confidentiality and security of the data.

Special consideration should be given to how the confidentiality of SSNs can be protected. If SSNs will be stored on paper or electronically, the list of SSNs must be cross-referenced with a unique study code number and without any cross-reference to the name of the individual. The list of SSNs must be locked in a secure location (i.e., cabinet) that is in a separate area from the location of the study data. If SSNs will be stored electronically, the SSNs should be stored separately from the drives/disks that store the research data. Electronic storage of SSNs must apply the highest level of data security. One recommended method to further protect the confidentiality of SSNs is to “hash” the numbers. Hashing is a technical term for disguising a number within a larger number. For example, a SSN of 123-456-7890 may be hashed when it has been incorporated in a number such as 49812398345623789055. For more information, you should consult with CUMC Information Technology (http://www.cumc.columbia.edu/it/about/service_desk/).

The IRB has a policy on [Disclosure of Social Security Numbers Outside of Columbia for Research Purposes](#) (the **SSN Disclosure Policy**). If SSNs will be shared with individuals outside of the Columbia study team (e.g., the sponsor), additional justification for such a release must be provided in the IRB submission. Generally, Columbia will not allow release of SSNs to other organizations as the ability to protect the confidentiality of such information is outside Columbia’s control. Disclosure will be permitted only when there is no alternative acceptable method for achieving the research objectives and when the risk of harm from inadvertent disclosure has been minimized through a required set of assurances and is justified by the potential benefit of the research. Therefore, the justification for such a release must be well supported and the confidentiality of the SSNs must be documented in a data use agreement approved by the IRB. Additionally, the informed consent document must explicitly state that SSNs will be disclosed outside of Columbia; a check-off box that the subject agrees to the release of his/her SSN to the external organization is recommended. The proposed use must be approved by both the IRB and the institutional official designated in the SSN Disclosure Policy. A Privacy and

Security Agreement as described in the SSN Disclosure Policy must be executed in most situations; use of SSNs for inquiries to the National Death Index is an exception.

F. Subject Compliance and Retention

In order to obtain valid study results, the subjects must adhere to the protocol requirements. It is very important that study subjects are as compliant as possible during the trial. It is also important that all compliant subjects be retained throughout the study, unless health considerations dictate otherwise.

1. Subject Compliance

Reasons for Noncompliance

The following are the most common reasons for subject non-compliance:

- Confusion about medication schedule
- Adverse reactions
- Failure to fill prescriptions or take medications
- Taking non-study medications when such medications are not permitted
- Scheduling difficulties (e.g., transportation, child care)
- Mental condition

Managing Compliance

Because the CRC is the member of the research team that has the most subject contact, his/her role in encouraging compliance is crucial. Some of the following suggestions may be helpful:

- Be sure to communicate effectively with subjects about study requirements and the importance of adhering to them.
- Schedule visits and procedures well in advance.
- Send reminder postcards and telephone calls preceding visits.
- Thoroughly question subjects about compliance at each visit.
- Let the subjects know that you are available by phone to answer questions.

Non-Compliance

If the CRC is aware that a subject has been non-compliant, he/she should inform the PI. Details of non-compliance should be documented in the site's source documents and CRFs. If the subject continues to be non-compliant, he/she may be removed from the study.

2. Subject Retention/Attrition

Reasons for Attrition

There can be many reasons why subjects drop out of a study, but some of the most common are:

- Failure to understand that he/she should remain in the trial even if symptoms abate
- Study requirements are too burdensome
- Side effects of medication
- Negative interactions with the research staff.

Tips for Retention

Some of the ways of retaining subjects are concrete, others relate more to the interaction of the subject with the CRC and other members of the research team. The following are examples of both:

- Observing and determining problems as early as possible
- Showing respect and communicating in an open fashion
- Giving the subject sufficient time to ask questions and answering them respectfully
- Showing concern for the subject as a human being (i.e., how is he/she feeling, how is the study going)
- If possible, rearranging the visit schedule to accommodate work/children
- Arranging transportation for a visit.
- Providing the subject with easy to read follow up schedules with date and time of each appointment and procedures, reminder cards and phone calls.
- Sending thank you notes and birthday cards.

When a research subject fails to appear for a research visit or procedure, the CRC must make diligent efforts to contact the subject by phone and mail in order to ascertain the reason for his/her absence and invite him/her to return to the site for study assessments. Records of all communications and attempted communications should be maintained in source documents. After vigorous attempts have been made to contact a subject, with no success, a subject may be classified as “lost to follow-up.”

Research subjects may, of course, decide to leave a study at any time. Although subjects are not obliged to give reasons for withdrawing prematurely from a trial, the CRC should make a reasonable effort to ascertain the reasons, while fully respecting the subject’s rights. See, e.g., ICH Guidelines for GCP (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464506.pdf)

When a subject withdraws from a study, the study sponsor should be notified promptly. This information must also be given to the IRB at the time of continuing review.

CHAPTER XI: SOURCE DOCUMENTATION AND CASE REPORT FORMS

A. Introduction

Obtaining, documenting and reporting study data accurately and fully is essential to maintaining data integrity. Data management includes: data collection, data entry, data verification and data validation. In clinical research, data is entered into and maintained in source documentation. Collected information is transcribed from data sources onto CRFs that are designed to record all of the information necessary to analyze the research study.

B. Source Documentation

Source data are all information contained in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the evaluation of the trial. Source data are contained in source documents, which may include hospital records, clinical and office charts, laboratory reports, memoranda, subjects' diaries, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, radiology and other ancillary service reports, subject files, patient visit notes, encounter forms, operative notes, patient medication diaries and electronic medical records. See ICH Guidelines for GCP (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM464506.pdf)

For FDA-regulated trials, adequate and accurate source documentation is required. According to [21 CFR 312.62\(b\)](#), an investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the CRFs and supporting data including, for example, signed and dated consent forms and medical records such as progress notes of the physician, the individual's hospital chart(s) and the nurses' notes. The case history for each individual should document that informed consent was obtained prior to participation in the study.

Good source documentation has several characteristics. Standard guidelines for good source documentation are termed "ALCOA". Under ALCOA, data must be:

- **Attributable.** The source document must show clearly who completed it. This will confirm that the appropriate personnel on the Delegation of Authority Log performed the study activity.
- **Legible.** Source documents must be able to be easily read.
- **Contemporaneous.** Source documentation should be recorded at the time the activity is performed to ensure accuracy.

- **Original.** The original data source must be maintained with study records. “Original” is typically defined to be the first record made by the appropriate person. The FDA permits the original document and the original data recorded on such document to be replaced by copies provided that the copies have been verified by a dated signature as being an exact copy of the original. See FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations (May 2007)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>.
- **Accurate.** Source documentation must conform to fact. It must be free of errors.

If these guidelines for source documentation are met, that data should lead to valid conclusions and reproducible results.

CRCs must provide direct access to source data and documents for trial-related monitoring, audits, IRB reviews and regulatory inspections.

<http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf>

C. CRFs

CRF completion constitutes a large portion of a CRC’s workload. The CRC should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs. Data reported on the CRF, which are derived from source documents, should be consistent with the source documents and across CRFs. Discrepancies, if any, should be explained.

Any change or correction to a CRF should be documented by drawing a single line through the incorrect entry (so it remains legible) and adding the correct entry, date and initials. If an explanation is necessary, this information should be included. This applies to both written and electronic changes or corrections. Sponsors will often provide guidance to CRCs regarding data corrections.

For training and sample CRF guidelines of the NIH, see https://ipocr.nihtraining.com/handouts/2011/St.Germain2_2012.pdf.

In order to address documentation errors, many sponsors have a query resolution procedure. Monitors will generate a data query in written or electronic form. A query is a data-related question, verification or request for further information that attempts to identify questionable, unclear or missing data within the CRF. CRCs must address the query, either by changing the original data as per the query or adding an explanation as to why the original data was correct. At times, the query may not be answered reliably; in this case, the CRC may provide the answer “unknown.”

D. Electronic Data Capture (EDC)

Many sponsors utilize EDC to collect clinical data in electronic format. One type of EDC is the electronic case report form, whereby clinical data is entered directly into a database. Typically, EDC systems provide a graphical user interface for data entry and a validation tool to check user data. The validation tool is particularly useful due to the fact that queries are generated immediately, providing valuable feedback for CRCs.

E. NYP “Do Not Abbreviate” Policy

NYP has identified a list of abbreviations that are frequently misinterpreted and if misinterpreted could affect patient safety. The abbreviations listed in the Do Not Abbreviate list may not be used in any part of the official medical record, including medical orders, progress notes, operative and procedure records and discharge and ambulatory records. To the extent such records are used in research, such as in chart notes or CRFs, the policy must be followed.

The current Do Not Abbreviate list is as follows:

Abbreviation	Definition	Term to Use
U	Unit	Unit
IU	International Unit	International Unit
OD	Once daily	Once daily
QOD	Every other day	Every other day
Trailing zero (X.0 mg) or lack of leading zero (.X mg)		Never write a zero by itself after a decimal point (X mg) and always use a zero before a decimal point (0.X mg)
MS, MSO+	Morphine Sulfate	Morphine Sulfate
Mg SO+	Magnesium Sulfate	Magnesium Sulfate

CHAPTER XII. DATA AND SAFETY MONITORING

A. Introduction

Data and safety monitoring is the process of reviewing data from an ongoing study to ensure the continuing safety of current and future participants, as well as the continuing validity and scientific merit of the study. Monitoring can be accomplished by the PI or a Data and Safety Monitoring Committee (also known as a Data Monitoring Committee or a Data and Safety Monitoring Board) generally pursuant to a Data and Safety Monitoring Plan. In addition, many industry sponsors utilize clinical research associates or other monitors to visit clinical research sites to help with study conduct, data integrity and study materials.

B. Data and Safety Monitoring

The principles of monitoring data and safety established by the NIH are the following:

- All clinical trials require monitoring
- Monitoring should be commensurate with the risk, size and complexity of the study

See NIH Policy for Data and Safety Monitoring (June 10, 1998)

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>.

Although written primarily for industry sponsors, the FDA's [Guidance for Industry: Oversight of Clinical Investigations – A Risk Based Approach to Monitoring](#) (August 2013) contains many helpful suggestions on proper monitoring of clinical investigations.

1. Data Safety and Monitoring Plan (DSMP)

The purpose of a DSMP is to ensure that a clinical trial has a system for appropriate oversight to ensure subject safety and data integrity. The plan should fit the complexity and risk profile of the protocol. The key elements of a DSMP are:

- Risk considerations
- Adverse event/unanticipated problem reporting
 - Who will report
 - To whom will the report be sent
 - What adverse event language and attribution criteria will be used to determine whether an event is adverse (adverse event definition, Common Toxicity Criteria)
 - Who will make the attribution decision
- Safety Monitoring
 - Who will monitor
 - How often and what criteria will trigger a change in frequency

- Who is authorized to unblind a study subject
- How will protocol deviations be handled
- What are the stopping points
- Data integrity
 - How will data quality be ensured
 - Who will collect the data
 - How will records be maintained

The Columbia IRB requires every clinical trial to have a DSMP.

For oncology studies at Columbia, please refer to the NCI Policy for Data and Safety Monitoring of Clinical Trials (June 22, 1999)

http://rrp.cancer.gov/clinicalTrials/data_safety_monitoring_plan.htm and the HICCC DSMP (July 31, 2013)

<http://www.hiccc.columbia.edu/sites/default/files/uploads/DSM%20Plan%20HICCC%20-%20CA013696.pdf>

2. Monitoring Responsibility

All clinical trials require data and safety monitoring, but not all trials require monitoring by a formal committee that is external to the sponsor or investigators. Monitoring can be done by the following individuals or groups:

Principal Investigator

The PI is always responsible for ensuring that the protocol is followed, the data is accurate and the research subjects are safe.

Clinical Research Associate (CRA) or Other Sponsor Monitor

Most industry sponsored trials will be monitored by a CRA or monitor who works for the sponsor or a CRO. The primary role of the CRA and monitor is to verify data integrity and compliance with the protocol through review of source data/CRFs and site visits. CRAs and monitors generally provide a written report after each site visit.

Monitoring visits are routinely scheduled and should be seen as a learning experience for CRCs.

Please note that it is University policy that external auditors are not permitted access to any electronic medical records (**EMR**) (e.g., Crown, iNYP, Eclipsys). See FPO Policy 1.15: CROWN Access for non-Columbia Doctor and/or Non-Columbia University Individuals.

Data and Safety Monitoring Committee (DSMC)

A DSMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. DSMCs were initially used primarily in large randomized multicenter trials sponsored by federal agencies such as the NIH. Pharmaceutical companies now routinely use them.

The NIH specifically requires the establishment of a DSMC for multi-site clinical trials involving interventions that entail potential risk to subjects, and generally for Phase 3 clinical trials. Although Phase 1 and Phase 2 clinical trials may also use DSMCs, alternative monitoring plans may be appropriate. For multi-site Phase 1 and Phase 2 trials, investigators should organize a central reporting entity to prepare reports on adverse events for distribution among sites and the IRBs of participating sites.

The FDA recommends that sponsors use DSMCs in the following situations:

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion.
- There are priori reasons for a particular safety concern (e.g., a particularly invasive treatment).
- There is prior information suggesting serious toxicity with the study treatment.
- The study is being performed on a potentially fragile population (e.g., children)
- The study is being performed on a population at elevated risk of death or other serious outcomes.
- The study is large, of long duration and multi-center.

See FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trials Data Monitoring Committees (March 2006)

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf>

The fundamental charges to a DSMC in monitoring a study are (a) to safeguard the interest of study participants, (b) to preserve study integrity and credibility and (c) to facilitate the availability of timely and reliable findings to the clinical community.

DSMCs typically operate under a written charter that includes well-defined standard operating procedures on meetings, presentation of data, access to interim data, conflict of interest, etc.

DSMC analyses can be performed on blinded or un-blinded data, although it is preferable that the DSMC have access to un-blinded data so as to enable the earliest detection of evidence that may show a study to have a negative benefit-to-risk profile. After analyzing the agreed upon data, the DSMC may provide recommendations to the study investigators and sponsor about modifications in study design or in procedures for data management, quality control or reporting. DSMCs typically issue a report concluding whether or not the study should be continued. A recommendation to terminate the trial

would be made if the DSMC judged the results to be convincingly positive or negative or if it concluded that the study would be unable to conclusively answer the primary questions it was designed to address. DSMCs can issue an “open” report showing aggregate data, while maintaining a “confidential” report that contains confidential data, un-blinded statistics and individual interviews.

Items typically reviewed by a DSMC include study regulatory files, CRFs, tracking logs, informed consent documents and study source documents.

At the time of continuing review for a clinical trial, the IRB expects that the most recent report from the DSMC will be attached to the renewal submission. When it is not available, an explanation must be provided.

CHAPTER XIII. UNANTICIPATED PROBLEM, ADVERSE EVENT AND PROTOCOL DEVIATION/VIOLATION REPORTING

A. Introduction

Reporting on safety during a clinical trial is one of the most important tasks of the PI and the CRC. The regulations in this area are confusing because two regulatory agencies – HHS and the FDA – have different, but conceptually overlapping, reporting requirements. Both HHS and the FDA have Guidances relating to reporting to the IRB; the FDA has additional Regulations and a Guidance relating to reporting to sponsors and the FDA when an IND or IDE is involved. The FDA also has Regulations relating to safety reporting in bioavailability (**BA**) and bioequivalence (**BE**) studies. This chapter will describe the different reporting requirements relating to each, for both investigators and S-Is. In addition, it will discuss protocol deviations and violations, including reporting responsibilities relating to them.

B. Reporting to the IRB

1. Federal Guidances

As described below, the key concepts in understanding safety reporting to the IRB are **Unanticipated Problems** and **Adverse Events**. There are currently the following federal Guidances on the topic of reporting Unanticipated Problems and/or Adverse Events:

- HHS: Guidance on Reviewing and Reporting Risks to subjects or Others and Adverse Events (January 15, 2007) (the **HHS IRB Guidance**) <http://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html>
- FDA: Draft Guidance on Adverse Event Reporting (April 9, 2007) (the **2007 FDA IRB Guidance**) <http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0106-gdl0001.pdf> and Guidance for Clinical Investigators, Sponsors and IRBs – Adverse Event Reporting to IRBs – Improving Human Subjects Protection (January 2009) (the **2009 FDA IRB Guidance**) <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2007-D-0202-gdl.pdf> .

It is helpful when trying to distinguish between Unanticipated Problems and Adverse Events to put the analysis into historical context. The FDA has for many years required investigators to report in clinical trials involving an IND the occurrence of any “adverse event” (See, e.g., [21 CFR 312.64](#)) and the concept of adverse event has been used generally in reporting to sponsors. At the same time, both the HHS regulations and the FDA regulations required that “unanticipated problems” be reported by the investigator to his/her institutional IRB. (See, e.g., [45 CFR 46.103\(b\)\(5\)](#) and [21 CFR 56.108\(b\)](#)). However, neither the HHS nor the FDA regulations defined what was meant by either term.

Over time, both HHS and the FDA realized that IRBs were being inundated by adverse event reports. As stated in the 2009 FDA IRB Guidance, the “FDA developed this guidance in response to concerns raised by the IRB community...that increasingly large volumes of individual adverse event reports submitted to IRBs – often lacking in context and detail – are inhibiting rather than enhancing, the ability of IRBs to protect human subjects” (2009 FDA IRB Guidance, Section I). Both agencies therefore sought to formulate concepts that would **limit** the adverse event reporting to the IRB, while making the reporting more meaningful.

HHS and the FDA provide definitions in their Guidances of Adverse Events and Unanticipated Problems that are consistent but not identical.

The HHS IRB Guidance defines Adverse Events and Unanticipated Problems, as follows:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom or disease, temporally associated with the subject’s participation in research, whether or not considered related to the subject’s participation in the research (HHS IRB Guidance, Section II). The definition of Adverse Event is modified from the definition of adverse event in the ICH GCP Guidelines (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf).

Unanticipated Problem (UP) is any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized (HHS IRB Guidance, Section I).

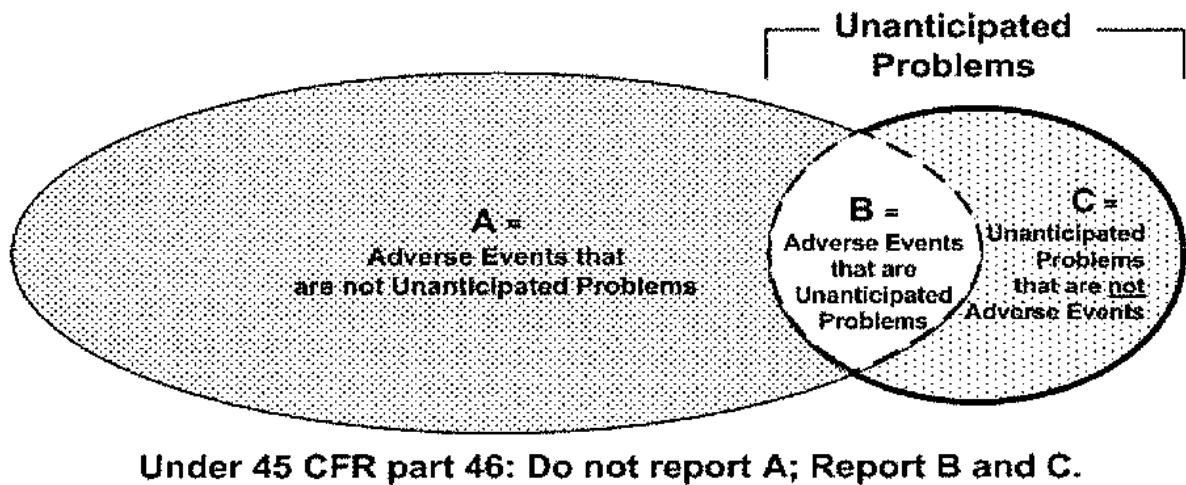
HHS notes that an incident, experience or outcome that meets the three criteria in the definition of UP generally will warrant consideration of substantive changes in the research protocol or informed consent document or other corrective action, which is the proper role of an IRB, whether the incident is an adverse event or not.

The FDA recognizes that its regulations use different terms when referring to an adverse event, such as “adverse effect” ([21 CFR 312.64](#)) and “adverse experience” ([21 CFR 312.32](#)) and considers the term “adverse event” to incorporate both. See the 2009 FDA IRB Guidance, Section I.

The FDA believes that only the following AEs should be considered as UPs:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure
- A single occurrence, or a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure
- Multiple occurrences of an AE that, based on an aggregate analysis, are determined not to be isolated occurrences and involve risk to human subjects
- An AE that is described or addressed in the Investigator’s Brochure, protocol or informed consent documents (a **Described AE**), but occurs at a specificity or severity that is inconsistent with prior observations
- A serious Described AE, but for which the rate of occurrence represents a clinically significant increase in the expected rate of occurrence
- Any other AE or safety finding that would cause the sponsor to modify the Investigator’s Brochure, study protocol or informed consent documents or would prompt other action by the IRB to ensure the protection of human subjects (2009 FDA Guidance, Section III (A)).

HHS provides a diagram in the HHS IRB Guidance to help conceptualize the relationships between AEs and UPs:



The diagram illustrates three key points:

- The vast majority of AEs occurring in human subjects are not UPs (Area A).
- A small proportion of AEs are UPs (Area B).
- UPs include other incidents, experiences and outcomes that are not AEs (Area C).

The key question regarding a particular AE is whether it meets the criteria set forth in the HHS IRB Guidance or the 2009 FDA IRB Guidance, both of which include examples of AEs and UPs.

2. Columbia Policy

Columbia has incorporated the Guidances in a [Policy on Reporting to the IRB of Unanticipated Problems Involving Risks](#). Only AEs that meet the UP criteria must be reported to the IRB. As mandated by HHS and FDA regulations, reporting is required both at the time of the occurrence of the problem ([45 CFR 46.103\(b\)\(5\)](#) and [21 CFR 56.108\(b\)](#)) and at the time of continuing review ([45 CFR 46.109\(e\)](#) and [21 CFR 56.109\(f\)](#)).

At the time of the Occurrence of an Unanticipated Problem:

Each UP should be reported to the IRB, whether or not (a) it is serious or non-serious or (b) it occurs at a site at which a Columbia investigator is conducting the research (an **Internal Site**) or a site at which a non-Columbia investigator is conducting the research (an **External Site**).

The UP should be reported promptly, but not later than one week following the occurrence of the UP or the PI's acquiring knowledge of the UP including, for External Sites, the determination that the occurrence meets the UP criteria.

For research conducted at an Internal Site, the Columbia investigator should make the determination as to whether an incident, experience or outcome constitutes a UP.

For research conducted at an External Site, an incident, experience or outcome generally should be reported to the IRB **only** if a monitoring entity (e.g., a DSMC) or an External Site investigator has determined that it constitutes a UP and so notifies the Columbia investigator.

Each UP should be reported to the IRB using the Unanticipated Problem Report module in Rascal, whether or not the UP occurred at an Internal Site or an External Site. If the latter, any report received by the Columbia investigator with respect to the UP should be attached in Rascal.

The investigator must conclude in the Unanticipated Problem Report whether the protocol and/or consent form(s) should be modified as the result of the UP. If the protocol and/or consent document(s) requires a revision, a modification must be submitted in Rascal.

At the Time of Continuing Review of a Protocol:

At the time of continuing review of a protocol, a Columbia investigator should submit a summary of all UPs that occurred during the review period and since the beginning of the study. The summary for each UP should include:

- The number of subjects who experienced the UP;
- The investigator's determination as to whether or not the UP was serious; and
- The investigator's determination as to the UP's relationship to the study procedures (e.g., definitely related, probably related or possibly related).

If the study is a multi-center study and is subject to oversight by a monitoring entity, a current report from the monitoring entity may be submitted in lieu of the summary of UPs described above. The current monitoring report must indicate the date of the review and the monitoring entity's assessment of the data reviewed. If not described in the DSMP submitted to the IRB, the report should also identify what information was reviewed.

Any monitoring entity reports that have not been previously submitted to the IRB should also be included with the continuing review submission. (Note that such reports should be routinely reported promptly to the IRB and submitted in Rascal as a modification to the protocol if a submission for continuing review will not occur within 30 days of the receipt of a monitoring entity report.)

The summary or the monitoring entity report should be attached as a separate document in Rascal that is clearly identifiable as a summary relating to UPs or a recent monitoring report.

In either case, the IRB will review the report to determine whether the protocol and/or consent documents should be revised. In addition, the IRB may impose restrictions on the research (e.g., more frequent reporting, suspension of enrollment, suspension of the study, termination, etc.) if review of Unanticipated Problem Reports results in a determination that the risk/benefit ratio has become less favorable. When a UP results in a change to a protocol or consent form that is initiated by a Columbia PI, reporting the UP to OHRP and, if applicable, the FDA is required.

See the HHS IRB Guidance and the 2009 FDA IRB Guidance for a more detailed discussion of reporting requirements.

C. Reporting to the Sponsor and/or the FDA

The FDA has separate safety reporting requirements for IND studies and IDE studies. The FDA has issued the following Regulations and Guidance:

- Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (September 28, 2010) (the **2010 FDA Regulations**)
<https://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf>
- Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012) (the **2012 FDA Guidance**)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>

The 2010 FDA Regulations amend only certain sections of 21 CFR relating to IND studies and BA and BE studies.

The FDA believed that the new regulations were necessary because, under the pre-existing regulations, sponsors were frequently reporting, as individual cases, serious adverse experiences

for which there was little reason to believe that the subject drug caused the event. The FDA saw the tendency to default to reporting an uninformative individual case to have been primarily related to the misapplication of the *reasonable possibility* standard in the definition of *associated with the use of the drug* currently contained in [21 CFR 312.32](#). The FDA believed that the clarifications contained in the 2010 FDA Regulations would increase the likelihood that submitted information will be interpretable and will meaningfully contribute to developing a safety profile of the investigational drug. In addition, the 2010 FDA Regulations have been harmonized with international regulations.

Investigator Reporting Obligations (Section D) and S-I Reporting Obligations (Section E) below cover investigator and S-I reporting requirements, respectively.

D. Investigator Reporting Requirements

Investigators must report AEs and Serious Adverse Events (SAEs) to a monitoring entity (e.g., the sponsor, a coordinating or statistical center, an independent medical monitor or a DSMC) when required to do so by the sponsor protocol or by regulation. The primary reporting obligations are as follows:

FDA

For **IND Studies**, an investigator must report the following:

- **To the Sponsor, immediately**, any SAE, whether or not considered drug related by the investigator ([21 CFR 312.64](#))
- **To the Sponsor, in accordance with the protocol**, any **nonserious adverse event** ([21 CFR 312.64](#)), whether or not considered drug related by the investigator.
- **To the Sponsor, in accordance with the protocol**, any **study endpoint** that is a SAE ([21 CFR 312.64\(b\)](#))
- **To the Sponsor, immediately**, any **study endpoint** when there is evidence suggesting a causal relationship between the drug and the event ([21 CFR 312.64\(b\)](#)).

As defined in the 2010 FDA Regulations:

Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related ([21 CFR 312.32\(a\)](#)).

The 2012 FDA Guidance states that an AE (also referred to as an adverse experience) can be any unfavorable and unintended sign, symptom or disease temporarily associated with the use of a drug, without any judgment about causality.

Serious Adverse Event (SAE): an AE or Suspected Adverse Reaction (see **S-I Reporting Requirements: AEs and Suspected Adverse Reactions (Section E(2))** below is considered to

be a SAE if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

[21 CFR 312.64](#) provides that the investigator report of a SAE must include an assessment as to whether there is a **reasonable possibility** that the drug caused the event ([21 CFR 312.64\(b\)](#)). SAEs include events listed in the protocol or anticipated to occur in the study population independent of drug exposure or in the Investigative Brochure (**IB**) as predicted to occur with the drug unless an alternative reporting arrangement has been made under [21 CFR 312.32\(c\)\(3\)](#).

For further information on the reporting requirements, see the 2010 FDA Regulations at <http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf> and the 2012 FDA Guidance at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/UCM227351.pdf>.

For **IDE Studies**, an investigator must report the following:

- **To the Sponsor and the IRB, as soon as possible, but in no event later than 10 working days after the investigator learns of the event, any Unanticipated Adverse Device Effect ([21 CFR 812.150](#))**

Unanticipated Adverse Device Effect (UADE) is defined 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...or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

AEs and SAEs may be assessed according to their severity and relationship to the test article. Only personnel designated on the Delegation of Authority Log with the responsibility to assess AEs or SAEs may do so. At each study visit, CRCs should ask research subjects about the nature and duration of any medical occurrences and note all events in study source documents. For AEs or SAEs that are continuing, CRCs should inquire about their persistence at the next visit in order to assess duration. AEs and SAEs and their severity and duration must be carefully recorded in source documents.

Some AEs are known to accompany treatment with certain investigational products. For these AEs, sponsors will often include management guidelines in the protocol. If an investigator meeting is arranged, sponsor personnel may discuss management of known AEs. If the sponsor does not provide guidelines to manage AEs, investigators may rely on their clinical judgment

and may also consider referring research subjects to specialists. It is the investigator's responsibility to ensure that adequate medical care is provided to a subject for any AEs, including clinically significant laboratory values, relating to the trial. In addition, the investigator should inform a subject when medical care is needed for any current illness of which the investigator becomes aware.

It is important to document each AE and SAE and to whom it is reported on an Adverse Event/Serious Adverse Event Reporting Log. Examples of an Adverse Event /Serious Adverse Event Reporting Log can be found in **Annex F**.

Please note that NYP requires reporting of certain adverse events, serious adverse effects and sentinel events. Hospital Policies and Procedures Manual, <http://infonet.nyp.org/QA/HospitalManual/S120SeriousAdverseEvents.pdf> . See also http://www.mers-international.com/mers_usa.html. These policies apply whether the study subject is an inpatient at NYP or an outpatient in NYP's Ambulatory Care Network.

If the NCI has sponsored the investigational agent being used in a study, any serious or unexpected event must be reported on its web-based reporting system, ADEERS (Adverse Events Expedited Reporting System), that can be accessed at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm .

The following is a quick guide to investigator reporting obligations that are described in more detail above. Please note that additional reporting requirements may be imposed by the sponsor or any funding or drug/device source.

Reporting Obligations of INVESTIGATORS

DRUG	IRB¹	FDA	Sponsor²	Funding Source/Drug Source	Other Investigators	NYP⁴
Unanticipated Problem (UP)	Promptly, but no later than 7 days after occurrence or PI knowledge	n/a	As required by sponsor	As required by funding/drug source	n/a	Immediately
Adverse Event (AE)	n/a	n/a	Promptly (21 CFR 312.64)	As required by funding/drug source	n/a	n/a
Periodic	Annual renewal of protocol should include summary of all UPs reported.	n/a	n/a	n/a	n/a	n/a
Nonserious AE	n/a	n/a	In accordance with the protocol	As required by funding/drug source	n/a	n/a
Serious Adverse Event (SAE)	n/a	n/a	Immediately	As required by funding/drug source	n/a	n/a
Study endpoint that is a SAE	n/a	n/a	In accordance with the protocol	As required by funding/drug source	n/a	n/a
Study endpoint with causal relationship to drug	n/a	n/a	Immediately	As required by funding/drug source	n/a	n/a
DEVICE	IRB^{1,3}	FDA	Sponsor³	Funding Source/Device Source	Other Investigators	NYP⁴
Unanticipated problem (UP)	Promptly, but no later than 7 days after occurrence or PI knowledge	n/a	As required by sponsor	As required by funding/device source	n/a	Immediately
Unanticipated Adverse Device Effect (UADE)	As soon as possible, but no later than 10 working days after knowledge of UADE	n/a	As soon as possible, but no later than 10 working days after knowledge of UADE.	As required by funding/device source	n/a	Immediately

Periodic	Annual renewal of protocol should include summary of all UPs reported.	n/a	n/a	n/a	n/a	n/a
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¹<http://www.cumc.columbia.edu/dept/irb/policies/documents/UnanticipatedProblemsPolicy.FINALVERSION.012408.pdf>

²http://www.ecfr.gov/cgi-bin/text-idx?&node=se21.5.312_164; [For information on the 2010 FDA Regulations, see http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2010_register&docid=fr29se10-3.pdf]

³<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.150>

⁴<http://www.cumc.columbia.edu/dept/irb/policies/documents/NYPAEReportingpolicy.pdf>

E. S-I Reporting Obligations

1. Unanticipated Problems

A S-I should notify both the IRB and the FDA of any UP promptly, but no later than 7 days after the occurrence of the UP.

If the S-I is in charge of a multi-center trial, he/she is in a better position to analyze the significance of AE information from multiple sites and make a determination about whether an AE or series of AEs constitutes a UP. The FDA therefore puts the responsibilities for reporting UPs in multi-center studies squarely on the S-I.

2. AEs and Suspected Adverse Reactions

Under the 2010 FDA Regulations, a S-I must promptly review all information relevant to the safety of the drug obtained or otherwise received by the S-I from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or *in vitro* studies, reports in the study literature and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States ([21 CFR 312.32\(b\)](#)). This review is necessary to decide if an individual case of a serious and unexpected adverse event meets the criteria for reporting, as well as to evaluate all accumulating data at regular intervals to identify new safety signals.

For **IND Studies**, the S-I must report the following:

- **To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that information qualifies for reporting, in an IND safety report, any Suspected Adverse Reaction that is both serious and unexpected ([21 CFR 312.32\(a\)\(1\)\(i\)](#)).**

A **Suspected Adverse Reaction** is any AE for which there is a reasonable possibility that it was caused by the drug ([21 CFR 312.32\(a\)](#)).

Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE ([21 CFR 312.32\(a\)](#)). Examples of reasonable possibility provided by the 2012 FDA Guidance are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.

- An aggregate analysis of specific events observed in a clinical trial that indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

An AE or a Suspected Adverse Reaction is **serious** if, in the view of either the investigator or the sponsor, it results in one of the outcomes listed in the definition of a SAE ([21 CFR 312.32\(a\)](#)). See **Investigator Reporting Requirements: FDA (Section D)** above.

An AE or Suspected Adverse Reaction is **unexpected** if it is not listed in the IB or is not listed at the specificity or severity that has been observed or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application ([21 CFR 312.32\(a\)](#)).

- **To the FDA and all participating investigators, as soon as possible but no later than 15 calendar days after the S-I determines that the information qualifies for reporting**, any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies, whether or not conducted under an IND or by the S-I, that suggest a **significant risk in humans exposed to the drug** ([21 CFR 312.32\(c\)\(1\)\(ii\)](#)).
- **To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting**, any findings from animal or *in vitro* testing, whether or not conducted by the S-I, that suggest a **significant risk in humans exposed to the drug** ([21 CFR 312.32\(c\)\(1\)\(iii\)](#)).
- **To the FDA and all participating investigators, as soon as possible, but no later than 15 calendar days after the S-I determines that the information qualifies for reporting**, any **clinically important increase in the rate of a Serious Suspected Adverse Reaction** over that listed in the protocol or IB ([21 CFR 312.32\(c\)\(1\)\(iv\)](#)).
- **To the FDA, as soon as possible, but no later than 7 calendar days after the S-I's initial receipt of the information**, any **unexpected fatal or life-threatening suspected adverse reaction** ([21 CFR 312.32\(2\)](#)).

An AE or Suspected Adverse Reaction is considered **life-threatening** if, in the view of the S-I, its occurrence places the patient or subject at immediate risk of death ([21 CFR 312.32\(b\)](#)).

In addition, in each IND safety report, the S-I must identify all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and must analyze the significance of the Suspected Adverse Reaction in light of previous similar reports or any other relevant information.

For further information on the reporting requirements, see the 2010 FDA Regulations at <http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf> and the 2012 FDA Guidance at <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf>

The following is a quick guide to investigator reporting obligations when the investigator is acting as a S-I **in addition to those described in Investigator Reporting Obligations (Section D) above**. Please also note that additional reporting requirements may be imposed by any funding or drug/device source.

Reporting Obligations of SPONSOR-INVESTIGATORS

DRUG	IRB ¹	FDA ^{2,3}	Sponsor	Funding Source/Drug Source	Other Investigators ^{2,3,4}	NYP ⁷
Unanticipated Problem (UP)	Promptly, but no later than 7 days after occurrence or PI knowledge	n/a	n/a	As required by funding/drug source	n/a	Immediately
Adverse Event (AE)	n/a	n/a	n/a	As required by funding/drug source	n/a	n/a
Serious Adverse Event (SAE)	n/a	n/a	n/a	As required by funding/drug source	n/a	Immediately
Periodic	Annual renewal of protocol should include summary of all UPs reported.	Annual progress report for IND should include summary of all safety reports submitted.	n/a	Annual report as required	n/a	n/a
Serious and Unexpected Suspected Adverse Reaction	n/a	As soon as possible, but no later than 15 calendar days after S-I determination	n/a	As required by funding/drug source	Same as FDA	n/a
Any findings or tests that suggest a significant risk to humans	n/a	As soon as possible, but no later than 15 calendar days after S-I determination	n/a	As required by funding/drug source	Same as FDA	n/a
Increase in rate of Serious Suspected Adverse Reaction	n/a	As soon as possible, but no later than 15 calendar days after S-I determination	n/a	As required by funding/drug source	Same as FDA	n/a
Unexpected fatal or life-threatening Suspected Adverse Reactions	n/a	As soon as possible, but no later than 7 calendar days after receipt by S-I of information	n/a	As required by funding/drug source	Same as FDA	n/a

DEVICE	IRB ^{1,5}	FDA ⁵	Sponsor	Funding Source/Drug Source	Other Investigators ^{5,6}	NYP ⁷
Unanticipated Problem (UP)	Promptly, but no later than 7 days	n/a	n/a	As required by funding/ device source	n/a	Immediately
Unanticipated Adverse Device Effect (UADE)	As soon as possible, but no later than 10 working days after knowledge of UADE Results of 21 CFR 812.46 investigation: within 10 working days after sponsor first receives notice of UADE	As soon as possible, but no later than 10 working days after knowledge of Results of 21 CFR 812.46 investigation: within 10 working days after sponsor first receives notice of UADE ()	n/a	As required by funding/ device source	Conduct an immediate evaluation of any UADE. If UADE presents an unreasonable risk to subjects, investigation or parts of the investigation presenting that risk should be terminated as soon as possible, but no later than 5 working days after the sponsor makes this determination and result of evaluation reported within 10 working days after the sponsor first receives notice of the UADE.	Immediately
Periodic	Annual renewal of protocol should include summary of all UPs reported.	Annual progress report for IDE should include summary of all safety reports submitted.	n/a	Annual report as required	n/a	n/a

¹<http://www.cumc.columbia.edu/dept/irb/policies/documents/UnanticipatedProblemsPolicy.FINALVERSION.012408.pdf>

²http://www.ecfr.gov/cgi-bin/text-idx?&node=se21.5.312_132 [For information on the 2010 FDA Regulations, see http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2010_register&docid=fr29se10-3.pdf]

³http://www.ecfr.gov/cgi-bin/text-idx?&node=se21.5.312_156

⁴http://www.ecfr.gov/cgi-bin/text-idx?&node=se21.5.312_155

⁵http://www.ecfr.gov/cgi-bin/text-idx?&node=se21.8.812_1150

⁶http://www.ecfr.gov/cgi-bin/text-idx?&node=se21.8.812_146

⁷<http://www.cumc.columbia.edu/dept/irb/policies/documents/NYPAEReportingpolicy.pdf>

F. Safety Reporting for Bioavailability (BA) and Bioequivalence (BE) Studies

BA and BE studies are regulated by the FDA under [21 CFR 320](#). A BA study is one that tests the rate and extent to which an active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. A BE study is one that tests the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions.

The IND safety reporting requirements under [21 CFR 312.32](#) apply to BA and BE studies conducted under an IND. The safety reporting requirements under [21 CFR 320.31](#) apply to persons conducting BA or BE studies that are exempt from the IND requirements.

The person conducting a BA or BE study must notify the FDA and all participating investigators of a SAE, regardless of whether the event is considered drug related, observed during the conduct of the study, as soon as possible but no later than 15 calendar days after becoming aware of its existence.

If the AE is serious or life-threatening, the person conducting the study must also notify the Office of Generic Drugs in the Center for Drug Evaluation and Research at the FDA as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence.

For further information, see the 2010 FDA Regulations http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2010_register&docid=fr29se10-3.pdf and the 2012 FDA Guidance <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>.

G. Protocol Deviations and Violations

All requests for deviations from and reports of violations of IRB policies or IRB determinations, including departures from the requirement for adherence to the approved protocol, must be reported to the IRB.

A protocol **deviation** is defined as a divergence from the approved protocol, IRB policies or IRB determinations for one subject or to address a temporary situation that is identified by the research team and **approved by the IRB before implementation**.

A protocol **violation** is defined as a divergence from the approved protocol, IRB policies or IRB determinations that was **implemented without prospective approval by the IRB** and was not implemented to avoid or minimize imminent harm.

Procedures will vary based on whether a Columbia IRB is the IRB that has reviewed and approved the study (the **Reviewing IRB**). A non-Columbia IRB will be the Reviewing IRB

when Columbia has agreed to rely on a non-Columbia IRB for review and approval of the protocol through a reliance agreement.

1. Deviations

When a Columbia IRB is the Reviewing IRB

Requests for protocol deviations should be submitted via the Modification module in Rascal as soon as the study team becomes aware of the need for the deviation. For sponsored projects, approval from the sponsor should be provided with the Modification. For time-sensitive Deviation requests, the PI should follow his/her submission to the IRB with an e-mail outside of Rascal to the Manager of the IRB that approved the study.

If a modification to request a protocol deviation cannot be submitted because there is already a Modification or Renewal under review by the IRB, the investigator should consult the Manager of the applicable Columbia IRB for guidance.

Note that multiple, similar protocol deviation requests suggest that the protocol may need to be revised to accommodate such situations, particularly if additional deviations may compromise the safety of participants or the scientific integrity of the data.

When a Non-Columbia IRB is the Reviewing IRB

Requests for protocol deviations should be submitted to the Reviewing IRB in accordance with procedures established by the Reviewing IRB. Documentation of the request and the decision of the Reviewing IRB should be submitted in Rascal when available.

2. Violations

When a Columbia IRB is the Reviewing IRB

Each violation must be assessed by the study team to determine if it is a UP and, if it is not, whether it is a major or minor violation. The PI is responsible for making the initial assessment, in order to determine the manner and timing of submission to the IRB. The IRB will independently make these determinations during the review process, taking the PI's assessment into account.

If a protocol violation is unexpected, at least possibly relating to the research, and involves risks to subjects or others, it is considered a UP and must be reported to the IRB within one week (5 business days) using the UP functionality in Rascal. If the UP results in a modification to the protocol, consent form or other study related documents, those changes should be submitted as a Modification. Details are provided in the Columbia IRB Policy, Reporting to the IRB of Unanticipated Problems Involving Risks:

www.cumc.columbia.edu/dept/irb/policies/documents/UnanticipatedProblemsPolicy.FINALVERSION.012408.pdf. Note that not all UPs are violations.

Protocol Violations that are not UPs are categorized as minor or major violations.

Major Violations

Major violations are those that violate the rights or welfare of subjects, negatively affect the integrity of the study or result in a need for a change in the protocol or consent document(s). In most cases, they will be reported to the IRB as a Modification. However, when reporting of a major violation coincides with submission of a Renewal, the violation may be reported within the Renewal application.

The Modification submission to report a major violation should include the PI's assessment that the event does not meet the UP criteria.

Major violations must be reported to the IRB promptly, generally within one week (5 business days) of occurrence or, if it is not known to the PI at that time, of discovery by the PI, to provide an opportunity for the IRB to assess, within a reasonable timeframe relative to protection of subjects, whether the study should continue, and whether changes to study procedures are required.

Minor Violations

Minor violations are violations that are not UPs and do not meet the criteria to be considered major violations. These should be reported to the IRB at the time of continuing review, in a list or log that includes all UPs, deviations and major violations.

When a Non-Columbia IRB is the Reviewing IRB

Reporting of violations to a non-Columbia Reviewing IRB should be in accordance with the requirements of the Reviewing IRB.

At the time of the submission of a Renewal application in Rascal, in order to facilitate tracking of all local requirements and uploading of recent approval documents from the Reviewing IRB, an accounting of all violations that were reported to the Reviewing IRB should be provided, with documentation of the outcome of the Reviewing IRB's determinations.

At any time during the conduct of the study, if it is discovered that there is the potential for imminent harm to subjects, the investigator should implement any changes(s) necessary to reduce or remove such harm and subsequently submit a report of the situation via the Modification module so that such change(s) are documented and acknowledged by the IRB.

Information to provide, when a Columbia IRB is the Reviewing IRB, for Deviations and Violations

The description of the circumstances surrounding the deviation or violation should be clearly stated in the summary section of the Modification Information Form or in the Violation and/or Modification section of the Renewal Form, as applicable.

The following information should be included:

- A complete description of the deviation or violation;
- An explanation of why the deviation is necessary, or why the violation occurred;
- Whether the deviation affects, or the violation affected, the risk/benefit ratio for subjects, the integrity of the research data and/or subjects' willingness to continue as study participation;
- For protocol deviations, a plan to inform the subject if the deviation may change the subject's willingness to participate in the research study;
- When applicable, the sponsor's concurrence with the decision;
- If the deviation involves an Investigational Device under an IDE, documentation confirming that FDA approval has been obtained;
- If the deviation involves an IND, documentation that the FDA has been notified; and
- For protocol violations, a description of the measures that will be taken to correct or mitigate the situation or to prevent a recurrence of the same or similar violations.

Supporting documentation may be attached electronically and provided whenever available or pertinent.

XIV. FINANCIAL MANAGEMENT OF A STUDY

A. Introduction

At Columbia, although DAs have primary responsibility for the management of departmental or divisional financial matters, it is important for CRCs to have a basic understanding of the University's financial policies – particularly as they relate to sponsored projects – and to be fully knowledgeable of the financial matters that directly impact the running of clinical research.

Because financial compliance in the context of sponsored research involves many regulatory and policy implications, and because the University's financial systems are complex, this chapter will direct the reader to available resources that describe both, while focusing more directly on certain topics that are particularly relevant to clinical research.

B. Resources

The University has numerous websites and other resources that provide information on financial procedures and compliance. The most relevant of these are the following:

1. Sponsored Projects Handbook

As indicated in **Introduction: Purpose of Handbook (Chapter I, Section A)**, the **Sponsored Projects Handbook** provides practical guidance to academic personnel and administrative staff in the management of sponsored projects funded by both governmental and private organizations, and lays out the research policies and procedures of the University in this area. Of particular relevance for financial compliance are:

- **Preparing a Sponsored Project Budget (Chapter V)**
- **Financial Management of a Sponsored Project (Chapter VIII)**
- **Closing Out a Sponsored Award (Chapter X)**

2. CUMC Administrators' Manual

The purpose of the [CUMC Administrators' Manual](https://admin-manual.cumc.columbia.edu/administrators-manual) is to guide P&S DAs in their day-to-day work and to serve as a reference for all administrative staff at the University. It covers a wide range of DA activities, and discusses 15 topics in all. It can be found at <https://admin-manual.cumc.columbia.edu/administrators-manual>

The topics in the Manual most relevant to CRCs are:

- Section 3: [Patient Care Administration](#) summarizes policies and procedures associated with patient care operations and financial management and addresses regulatory and legal issues.

See in particular:

- Section 3.8: [Billing Compliance](#)
- Section 3.10: [Financial Management](#)
- Section 5: [Sponsored Project Administration](#) provides a description of the essential elements of sponsored projects administration from finding funding to close out of award. It relies heavily on the Sponsored Projects Handbook.
- Section 9: [Financial Management](#) provides guidance and procedures starting with internal controls and authorities, and covering routine financial management and reporting.

See in particular:

- Section 9.2: [Key Resources and Policies](#)
- Section 9.6: [The University Ledger System](#)
- Section 9.7: [Financial Systems \(Applications\)](#)
- Section 9.12: [Expenses](#)
- Section 9.13: [Cash Management](#)

C. Expenditures and Invoicing

1. Non-Industry Sponsored Clinical Research

As charges are recorded on individual sponsored projects, Sponsored Projects Finance (**SPF**) seeks reimbursement for these costs from project sponsors. For most federal agencies, the University has established letters of credit that permit the immediate transfer of funds. Otherwise, SPF prepares the requisite invoices. What backup documentation is required is determined by the sponsor.

Any charges on a sponsored project must be allowable, allocable, reasonable and within the study budget. The CRC, with the applicable DA, is responsible for monitoring the financial status of a project. The Sponsored Project Financial Report – Summary by Budget Category in ARC can be used, as it provides the current month and cumulative project-to-date expenditures of the project, as well as project budget information, displayed as totals by expenditure category. This report is useful in monitoring the current financial status of the project, for controlling the level of expenditures and for anticipating any potential financial concerns for the project.

For a more complete discussion of financial matters on non-industry sponsored projects, see **Financial Management of a Sponsored Project (Chapter VIII)** in the **Sponsored Projects Handbook**

2. Industry Sponsored Clinical Research

Study payments in industry sponsored trials are generally triggered by certain milestones such as specific activities (screening and enrollment), visits completed or CRFs completed. Because invoicing and reconciliation of industry sponsored research is so different from non-industry sponsored research, the CTO utilizes the StudyManager™ system to invoice industry sponsors for clinical trial activity. When the CTO executes a contract for a clinical trial, the CTO Budget Officer builds the study in StudyManager™, based on the Schedule of Events in the protocol and the budget. When study activity occurs (such as, a patient is screened or enrolled), the CRC logs it in StudyManager™. Then, the CTO invoices the sponsor for the activity according to the terms of the CTA.

CRCs are expected to enter study activity in StudyManager™ in order to support expeditious invoicing and payment. No CRC is authorized to invoice any industry sponsor; all invoicing must be done by the CTO.

D. Medicare

Because Medicare is a major payor of clinical costs, it is important to have some knowledge of the Medicare rules. The following policies determine which costs are reimbursable by Medicare:

Medicare Policy on Routine Costs in Clinical Research

Medicare covers the costs of items and services (routine costs) in qualifying clinical trials.

- **Qualifying Clinical Trials.** Qualifying clinical trials are those that meet the following three requirements:
 - The subject or purpose of the trial is the evaluation of an item or service that falls within a Medicare benefit category (e.g., physicians' service, medical equipment, diagnostic test) and is not excluded from coverage (e.g., cosmetic surgery, hearing aids).
 - The trial is not designed exclusively to test toxicity or disease pathophysiology. It has a therapeutic intent.
 - Trials of therapeutic interventions enroll patients with diagnosed diseases rather than healthy volunteers. Trials of diagnostic interventions may enroll healthy patients in order to have a proper control group.

The three requirements above are insufficient by themselves to qualify a clinical trial for Medicare coverage of routine costs. To qualify, clinical trials must also have the following characteristics:

- The principal purpose of the trial is to test whether the intervention potentially improves the participants' health outcomes;
- The trial is well-supported by available scientific and medical information or is intended to clarify or establish the health outcomes of interventions already in common clinical use;
- The trial does not unjustifiably duplicate existing studies;
- The trial design is appropriate to answer the research question being asked in the trial;

- The trial is sponsored by a credible organization or individual capable of executing the proposed trial successfully;
- The trial is in compliance with federal regulations relating to the protection of human subjects; and
- All aspects of the trial are conducted according to the appropriate standards of scientific integrity.
- **Routine Costs.** Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries that are provided in either the experimental or the control arms of a clinical trial **except** the following items and services:
 - The investigational item or service, unless otherwise covered outside of the clinical trial.
 - Items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan).
 - Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

Routine costs in clinical trials include:

- Items or services that are typically provided absent a clinical trial (Standard of Care).
- Items or services required solely for the provision of the investigational item or service. For instance, the *administration* of a non-covered chemotherapeutic agent is covered, while the agent is not.
- Clinically appropriate monitoring of the effects of the item or service.
- Activities required to prevent complications secondary to the agent, device or service.
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service (particularly for the diagnosis or treatment of complications).

In addition to covering routine costs in qualifying clinical trials, Medicare also covers reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials.

See, generally, <http://www.cms.hhs.gov/ClinicalTrialPolicies/> and the OBC training materials (<http://www.cumc.columbia.edu/dept/compliance/research.html>).

Medicare Coverage of Investigational Devices

It is University policy that investigational device studies under an FDA-issued IDE that begin with the letter “G” and post-market approval studies or registries of carotid stents must be submitted to NGS or CMS for a coverage decision prior to enrollment of subjects in the study.

See also **Preparing for a Study: Review and Finalization of Proposals and Contracts: Approval Process – Additional Approvals and Certifications-National Government**

**Services (NGS) or Centers of Medicare and Medicaid Services (CMS) Determination
(Chapter VI, Section D(2)).**

XV. STUDY CLOSURE

A. Introduction

There are many reasons for study closure, ranging from completion of the study to lack of enrollment to inefficacy of the test article. The PI is responsible for the programmatic and operational close out of a sponsored project, as well as all financial reconciliations and it is likely that the CRC will assist him/her in these tasks. Whatever the reason for the closure, the CRC must follow the proper procedures for closing the trial, both internally and externally with the sponsor.

B. Reasons for Study Closure

The most frequent circumstance for study closure is that it is complete: enrollment has stopped, all subjects have finished their participation in the study and the data are complete, accurate and analyzed. Remember that even if all patients have been seen, a study should not be closed until all follow up has been completed and all data collected and analyzed.

Studies may be closed before they are complete, either for positive reasons (e.g., the treatment is so beneficial that it would be unethical to not have all of the subjects receiving the treatment) or, more likely, negative reasons (e.g., the investigational product was found to be unsafe or ineffective or there is insufficient enrollment).

If the study is stopped abruptly while subjects are still taking the test article, a sponsor typically creates an orderly plan for discontinuing each subject and communicates this plan to each PI. In addition, if the treatment is blinded, the sponsor creates a plan for subject unblinding and communicates this to the PI. The CRC is instrumental in communicating this plan promptly to study subjects and assuring them of appropriate therapy and follow-up outside of the research study.

C. Closure Procedures

1. Programmatic

Technical Reports and Other Documentation

The PI is responsible for the submission of all technical reports as well as other agreed upon deliverables. All CRFs must be completed and submitted to the sponsor and any final queries from the sponsor resolved. Final reports must be given to federal agency sponsors, including the NIH and the FDA ([21 CFR 312.64](#)).

Test Article Reconciliation

At the end of the study, all drug supplies, including all containers of the study drug, whether empty or containing unused study drug, may be either returned to the sponsor or destroyed by the Research Pharmacy, according to the instructions in the protocol. A final inventory of the total amount of drug received at each study site against the amount used and returned will be maintained by the Research Pharmacy.

Upon completion or closure of a study involving an investigational device or the investigator's part of a study, or at the sponsor's request, the PI must return to the sponsor any remaining supply of the device or otherwise dispose of the devices as the sponsor directs ([21 CFR 812.110\(e\)](#)).

Study Close Out Visit

A study close out visit is a final monitoring visit conducted by the sponsor or CRA. Its objectives are as follows:

- To ensure that all CRFs have been completed
- To confirm that all CRFs have been submitted
- To review the status of all outstanding edits and queries
- To verify that a signed informed consent form is on file for each study participant
- To verify that all regulatory documents are up to date and maintained in the regulatory binder
- To confirm that the investigator and CRC have received and understand the requirements for retention of study records
- To conduct test article reconciliation
- To send unused and returned test articles to the sponsor, as applicable
- To confirm that all patient specimens have been shipped according to laboratory manual specifications

After the study close out visit has been conducted and all outstanding items have been completed, the sponsor or CRA will notify the site in writing that the site may be closed. Upon receipt of this letter, the CRC may initiate study termination with the IRB.

2. Financial

Closing Out a Sponsored Project Award (Chapter X) in the **Sponsored Projects Handbook** describes the responsibilities of the PI, DA and Sponsored Projects Finance (SPF) in closing out an award, including reconciliation of expenses and preparation of a final financial report. It also covers treatment of open commitments and encumbrances as well as post-closure issues, such as treatment of residual balances and overdrafts.

For those studies managed in the StudyManager™ system, CRCs must update all patient visits and procedures. When patient activity is complete in StudyManager™, the CTO does a reconciliation to ensure that all payments due to Columbia have been received. Once the study is closed, final payment has been received, and all outstanding obligations have been paid, CRCs should contact the CTO to close the account. This usually occurs after IRB closure.

3. IRB Closure

A Closure Report form must be submitted to the IRB when all study procedures are completed (including any analysis of identifiable data collected from the study by the Columbia researcher) and IRB approval of the project is no longer required.

Studies that were last reviewed by a full Board process will require the following information:

- Changes or amendments since the most recent approval (including changes in personnel since the most recent approval and additional information about risks associated with the study)
- Total number of participants in the study
- Number of participants since the most recent approval
- Number of participants who withdrew from the study, if applicable
- Number of participants who complained about the study, if applicable
- Summary of any recent literature or findings
- Brief summary of results.

<http://www.cumc.columbia.edu/dept/irb/documents/SOPVersion4.2November22012.pdf>

To close a study in Rascal, please follow these steps:

- Go to the Rascal home page at <https://www.rascal.columbia.edu>.
- Select 'My Rascal'.
- Log in with your UNI and password.
- Select 'My Protocols' under 'Human Subjects'.
- Select a protocol to view.
- Under 'Protocol Overview,' select 'Create Closure Report'.
- Complete Closure Report, attaching documents as needed.
- Select 'Save.'

4. Other Notifications

In addition to the IRB, one or more of the following Columbia offices should be notified of the study closure, as applicable:

- The CTO or SPA
- SPF
- Any reviewing entities (e.g., Radiation Safety)
- Departmental or divisional administrators
- Billing offices

5. Post Study Critique

Upon completion of a clinical trial, the CRC, investigator and other relevant personnel should meet to perform a post study critique. This critique should include assessment of the following study elements:

- Total subject enrollment. Was total subject enrollment in accordance with expectations? Was enrollment completed within the expected time frame?
- Summary of problems encountered. Did protocol deviations/violations take place? If so, how did the site correct these problems? How can future problems of this type be averted?
- Financial feasibility review. What were the costs associated with this study? Was it, in fact, economically feasible to conduct this study?
- Workload assessment. Was the workload required by this study reasonable? Was sufficient staff available to perform study assessments? Was test article accountability complicated?
- CRF assessment. Were the CRFs appropriate for the study? Were CRFs easy to complete?
- Sponsor interactions. Were communications with the sponsor acceptable?
- Patient considerations. Did site patient population benefit from study? Was this study desirable from a scientific standpoint?

The group should refer back to the feasibility assessment conducted at the beginning of the study that assessed resources, recruitment potential, financial feasibility and scientific integrity, to determine whether the initial feasibility assessment was in line with the final outcome. Overall, the group involved in the post study critique should evaluate the study outcome and review whether or not the site wishes to work with the same sponsor in the future.

D. Data Retention

The PI is responsible for storing regulatory documents, subject files and financial records for the period of time specified by law and the study sponsor. The costs of maintaining records should be included in the study budget. Recordkeeping requirements vary depending on whether the study was federally or industry funded, whether there are contractual provisions covering data retention or whether the protocol was conducted under FDA regulations.

The time period for maintaining research records in government sponsored studies is defined in various regulations. If multiple regulations apply to a particular study, the longest retention period applies. The required record retention period for industry sponsors is generally longer than those required by law and is generally included in the CTA as a contractual term.

1. FDA

INDs

The FDA IND regulations require an **investigator** to maintain the following records for 2 years following the date an NDA is approved for the drug or if no NDA is to be filed or if the NDA is

not approved, for 2 years after the investigation is discontinued and the FDA is notified (in either case, the **IND Retention Period**) ([21 CFR 312.62](#)):

- Adequate records of the disposition of the investigational drug, including data, quantity and use by subjects. At CUMC, these records are maintained by the Research Pharmacy.
- Adequate and accurate case histories that record all observations and other data pertinent to the investigation (e.g., CRFs, signed consent forms, medical records, etc.).

The FDA IND regulations require a **S-I** to keep adequate records showing the receipt, shipment or other dispositions of the investigational drug during the IND Retention Period ([21 CFR 312.57](#)). At CUMC, these records are maintained by the Research Pharmacy.

IDEs

The FDA IDE Regulations require an **investigator** to maintain the following records for a period of 2 years after the later of (a) the date on which the investigation is terminated or completed and (b) the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol (the **IDE Retention Period**):

- All correspondence with another investigator, an IRB, a monitor or the FDA, including required reports
- Records of receipt, use or disposition of a device
- Records of each subject's case history and exposure to the device
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
- Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation ([21 CFR 812.140\(a\)](#)).

The FDA IDE regulations require a **S-I** to retain the following records for the IDE Retention Period:

- All correspondence with another sponsor, a monitor, an investigator, an IRB or the FDA, including required reports
- Records of shipment and disposition of the device
- Signed investigator agreements including the financial disclosure information required to be collected under ([21 CFR 812.43\(c\)\(5\)](#)).
- For each investigation of a device other than a SR Device, the following records:
 - The name and intended use of the device and the objectives of the investigation;
 - A brief explanation of why the device is not a SR Device;
 - The name and address of each investigator;
 - The name and address of each IRB that has reviewed the investigation; and
 - Any other information required by the FDA.

- Records concerning adverse device effects (whether anticipated or unanticipated) and complaints
- Any other records that the FDA requires to be maintained by regulation or by specific requirement for a category of investigation or particular investigation ([21 CFR 812.40\(b\)](#)).

2. HHS

HHS regulations require that records relating to research be retained for at least three years after completion of the research ([45 CFR 46.115\(b\)](#)).

3. HIPAA

Because the HIPAA Rules give an individual the right to receive an accounting of any disclosures of PHI made during the six years prior to the request for the accounting, an investigator should keep study records, and records of all disclosures of study information, at least six years after the last subject has completed his or her participation in the study or the date of the last disclosure of identifiable health information from study records, if disclosures continue after all subjects have completed the study. See [45 CFR 164.528](#) for the specific data that must be retained.

See **Programmatic Management of a Sponsored Award: Retention and Access to Research Data (Chapter IX, Section D)** in the **Sponsored Projects Handbook** for additional information on retention of and access to research data.

A record of where study materials are stored must also be kept at the site. This will allow investigators and CRCs to locate records in case of an FDA audit.

XVI. AUDITS

A. Introduction

Audits are an expected part of clinical research. If the study involves an IND or IDE, the FDA may conduct an inspection of the site. Sponsors and IRBs may also conduct their own audits. This chapter will describe these audits, as well as the CRC role in audits, concentrating primarily on FDA audits, which are often the model for other audits.

B. Sponsor Audits

Sponsors, including governmental sponsors such as the NIH, may audit sites for several reasons. They may audit a site to ensure that the site is complying with federal regulations and with the protocol (**routine audit**), and they may also audit a site when there is evidence that the site is out of compliance with federal regulations or the protocol (**for cause audit**). Sponsors may also audit a site to ensure that sponsor representatives or CRAs are monitoring the site thoroughly.

Federal regulations support sponsor audits of all clinical investigations being conducted under the sponsor's IND. According to federal regulations, if a sponsor discovers that an investigator is not complying with the signed agreement (Form FDA 1572), the study protocol or federal regulations, the sponsor must take prompt action, including securing compliance by the PI. If the investigator does not comply, the sponsor should discontinue shipments of the test article to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor should require that the investigator dispose of or return the test article. In addition, the sponsor should notify the FDA ([21 CFR 312.56 \(a\) and \(b\)](#)).

A CRC should notify SPA or the CTO and the IRB if a non-industry sponsor announces an audit.

1. Routine Audits

Routine audits often occur because a sponsor believes that a particular site will be audited by the FDA. A sponsor may suspect that a site will be audited by the FDA either because it is a high enroller of subjects in the study or because multiple studies at the site contributed to the NDA.

For a routine audit, the sponsor will send an audit team that will follow the same inspection plan used by the FDA, as noted below. The sponsor audit team requires access to source documents, CRFs, the regulatory binder and test article dispensing/inventory records. If problems emerge during the course of an audit, the sponsor will direct the PI to remedy them. A report of the audit may or may not be provided to the site. This is because while FDA inspectors do not generally have access to sponsor audit reports, they do, during the course of an inspection, have access to investigator files.

2. For Cause Audits

For cause audits are done because of suspected noncompliance with federal regulations or with the protocol. The sponsor may not tell the site that the sponsor audit is a for cause audit. The sponsor audit team will inspect the same documents/elements of the study in a for cause audit as a routine audit; however, they will pay close attention to the areas of suspected noncompliance.

Several things could happen as the result of a sponsor audit. If the site appears to be in compliance, the results will be handled in the same manner as a routine audit. If the noncompliance was not found, but is still suspected, the sponsor may inform the FDA and ask them to investigate the site. If problems were found, they will either be corrected, or enrollment may be put on hold, or the study may be stopped at the site. In this case, the FDA may be informed.

C. IRB Audits

Because the IRB is responsible for overseeing the conduct of research that it approves, it may audit research studies on a not for cause basis. In addition, it may audit research in which faculty and/or staff of the University are engaged outside the institution.

IRB audits may be either routine or for cause. Routine audits are conducted to ensure that the site is conducting the study in compliance with federal regulations, the protocol and IRB policies. For cause audits are conducted in response to suspected noncompliance. The IRB reviews incidents of noncompliance and manages them in one of several ways depending on the severity of the noncompliance. A plan of corrective and preventative action is documented for each incident of noncompliance.

More information regarding Columbia's compliance oversight program is provided in the [Columbia University IRB Noncompliance Policy](#).

D. FDA Inspections

The FDA routinely performs inspections to evaluate study conduct and protocol adherence, collect data and assess regulatory compliance under its Bioresearch Monitoring Program (**BiMo**). The BiMo program is a comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research. The BiMo Program was established to assure the quality and integrity of data submitted to the agency, as well as to provide for protection of the rights and welfare of the thousands of human subjects involved in FDA regulated research.

See: <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm>

FDA inspections involve the evaluation of the investigator's or sponsor's practices and procedures to assess compliance with applicable regulations. The inspector will review informed consent forms in any inspection. When the inspection occurs as a result of FDA's receipt of a marketing application/submission, it will include a comparison of the data submitted by the sponsor to the FDA with source documents at the investigator's site (i.e., where original source data are recorded; also known as "supporting data") and CRFs in the investigator's files. If it is a

“for cause” or surveillance inspection of an on-going study, data comparison will generally involve only source documents and CRFs, because the FDA may not have data supplied by the sponsor. Source documents may include office records, hospital records, laboratory reports, records of consultations, etc. See www.fda.gov/oc/gcp/compliance.html.

FDA inspections may be either study related or investigator related. For either kind of audit, the inspection has three purposes:

- To determine the validity and integrity of the data
- To assess adherence to regulations and guidelines
- To determine that the rights and safety of the human subjects were properly protected.

The FDA has published a number of Compliance Program Manuals that are directed to FDA personnel, but are made available to the public. Because they include instructions to FDA staff in performing inspections, they provide invaluable information as to the intent, scope and data requirements of FDA inspections and should be reviewed in advance of any investigation. For access to these manuals, go to <http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm#drugs>.

1. Study Related Inspections

Study related inspections are usually done on studies that provide essential data for an NDA application. As noted above, those sites that contribute the most data, either by high subject enrollment or by conducting several studies at once, are most likely to be selected for this type of FDA audit. The sponsor will often alert sites that are likely to be contacted for FDA inspection and may send a CRA or sponsor representative to assist the site prepare for audit. If the FDA contacts a site to schedule an inspection, the site must inform the sponsor.

2. Investigator Related Inspections

Investigators may be selected for FDA inspections for a variety of reasons, including the following:

- An investigator has done a large number of studies
- An investigator has done work outside of his/her specialty areas
- An investigator has done a pivotal study that is critical to a new product application and it merits extra attention
- The safety and efficacy findings of an investigator are inconsistent with the results from other investigators working with the same test product
- The sponsor or IRB has notified the FDA about serious problems or concerns at the site
- There were an unexpected number of subjects with the diagnosis under study, given the patient population of the site
- Enrollment at the site was much more rapid than expected
- The study and investigator were highly publicized in the media.

3. Procedures

Site Preparation

When an inspection is planned, the site will usually be notified in advance. The FDA contacts the site by telephone to arrange a mutually acceptable time for a visit. Sites are usually given one or two weeks' notice; it is acceptable to negotiate a delay in the visit date, so long as the investigator has a good reason and the visit date is not extended too much. If the inspection is investigator-related, and if the FDA has concerns about subject safety or compliance, the inspectors may come unannounced.

If a PI or CRC receives notice that a FDA inspection has been scheduled or a FDA representative arrives at CUMC to conduct an unannounced inspection, the PI or CRC should immediately notify the IRB, the CTO (and, if applicable, SPA), the Office of the General Counsel and the sponsor (if applicable). The CTO and/or the IRB will review with the PI and CRC the required procedures to be followed during an inspection and will be available to provide assistance in preparing for the inspection.

Once an inspection is scheduled, sites should begin preparing by amassing all the study documents in one easily accessible location. CRCs should review the study documents to ensure that everything is accounted for, complete and well organized. Study documents that should be available for review include all informed consent forms, patient charts, test reports, laboratory reports, CRFs, the regulatory binder, AE and UP reports, all monitoring reports and all data available. Documents that are maintained in an EMR should be made available in paper format as it is University policy that external auditors are not authorized to access EMR systems. See **Data and Safety Monitoring: Data and Safety Monitoring – Monitoring Responsibility (Chapter XII, Section B(2))**.

Inspection Day Logistics

On the inspection day, the CRC should provide a quiet, spacious room for the FDA inspector to review records. All documentation should be ready for inspection. The role of the CRC in the audit is to be present or available at all times during the audit and to provide any necessary documents; the role of the investigator is to answer questions if asked. All University personnel should be polite, courteous, cooperative and reasonable; antagonism is inappropriate. The CRC should provide all the documents and other materials that the FDA inspector requests, but should refrain from giving the inspector free access to files or any University IT systems. All questions should be completely answered without going into extraneous detail.

Site personnel should not offer the inspector anything beyond a cup of coffee, such as a meal; this offer may be misconstrued as a bribe. At this time, the FDA is not privy to grant information or sponsor audit results; if the inspector asks for this information, the CRC should politely refuse to answer.

Inspection Day Process

The PI and the CRC should be available to meet with the FDA inspector when he/she arrives. The inspector will begin the audit by showing the CRC and the PI his/her credentials (photo ID card) as well as a Form FDA 482 (Notice of Inspection). If the inspector does not show these credentials, the CRC or the PI should request and review them.

During the inspection, the inspector will meet with the PI, the CRC and any other appropriate study staff and will review study documents. If individuals who played substantial roles in the study are no longer at the site, the investigator should be able to contact them, if at all possible, during the audit if the inspector wishes to talk to them. There are two main elements of the study that will be reviewed: study conduct and study data.

During an inspection at the site, FDA personnel typically verify the following elements of a study:

- Who performed various aspects of the protocol (e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data)
- The degree of delegation of authority (e.g., how the PI supervised the conduct of the investigation)
- How patients were enrolled, including obtaining proper informed consent
- Signatures on study documents
- Consistency of study data with source documentation
- How and by whom treatment was administered
- Where specific aspects of the investigation were performed
- How and where data were recorded and methodology applied
- Patient safety
- Accountability for the investigational product
- The monitor's communications with the PI
- The monitor's evaluations of the progress of the investigation
- How and by whom study end points were assessed.

See FDA Guidance for IRBs and Investigators, FDA Inspections of Clinical Investigators.
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf>

The FDA inspector will compare data that was submitted to the agency with the site records that support the data and, at times, will compare these groups of records with the sponsor's CRFs. The inspector will pay close attention to the following elements:

- Patient diagnoses
- Whether the patients were properly diagnosed based on their past history
- Whether or not subjects met the protocol inclusion/exclusion criteria
- Concomitant medications (in particular, prohibited concomitant medications)
- Appropriate follow up of adverse events.

The inspector may look at data for only a sampling of subjects, or, if there appear to be problems, he/she may look at the data from all subjects. All informed consent forms are usually reviewed.

The duration of a FDA inspection depends on the amount of data to review, the findings and the amount of time the inspector has available for the audit. The days may not be consecutive, but may be a day or two at a site until the inspection is completed.

At the end of the inspection, the inspector will meet with the investigator to review the audit findings. During this meeting, the investigator may ask questions about anything that is not understood, and you may clarify things the inspector has misinterpreted. Sometimes a misunderstanding or negative finding of the inspector can be explained satisfactorily at this point. If there are significant findings, the inspector may issue a Form FDA 483 (Notice of Observations) to the PI. The inspector will request a written response to each finding in the Form FDA 483, typically within 15 days.

Most sponsors ask that the PI call them after the inspector leaves and let them know the results of the inspection. If the PI has received a Form FDA 483, the sponsor will usually offer to help the PI formulate his/her reply. CTAs sometimes have a provision for reimbursement of audit-related expenses and/or time incurred by Columbia or the PI.

After the Inspection

After the inspection is complete, the FDA inspector prepares an Establishment Inspection Report. The PI will typically receive a copy of the report a few months after the inspection. This report is assigned one of the following compliance classifications:

- No action indicated (**NAI**). No significant deviations from the regulations were found. The PI is not required to respond to this report.
- Voluntary action indicated (**VAI**). This report provides information about findings of deviations. This letter may or may not require a response from the PI. If a response is required, the letter will specify what is necessary. Although this category is called “voluntary action”, the FDA recommendations should be followed by the research team.
- Official action indicated (**OAI**). This report identifies serious deviations from the regulations that require prompt action by the PI. For OAIs, the FDA may also inform the sponsor and the IRB. In addition, the sponsor may be notified by the FDA that the monitoring of the study was deficient. In addition to issues the warning letter, the FDA may take other action, such as regulatory and/or administrative sanctions against the investigator.

FDA Inspection Documentation

It is the responsibility of the PI to retain all correspondence and other documentation relating to FDA inspections. The IRB will maintain a master file of all such correspondence and documentation should be sent by the PI to the IRB for inclusion in the FDA master file.

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GLOSSARY OF ACRONYMS

AE	Adverse Event
ARC	Accounting and Reporting at Columbia
BiMo	FDA Bioresearch Monitoring Program
CDA	Confidentiality and Disclosure Agreement
CFR	Code of Federal Regulations
CMS	Centers for Medicare and Medicaid Services
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CTO	Clinical Trials Office
CTSA	Clinical and Translational Science Award
DA	Departmental Administrator
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
EDC	Electronic Data Capture
EH&S	Office of Environmental Health and Safety
FCOI	Financial Conflict of Interest
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDE	Humanitarian Device Exemption
HHS	Department of Health and Human Services
HICCC	Herbert Irving Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protection Office

HUD	Humanitarian Use Device
IAA	IRB Authorization Agreement
IACUC	Institutional Animal Care and Use Committee
IB	Investigator Brochure
IBC	Institutional Biosafety Committee
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
JRSC	Joint Radiation Safety Committee
NCI	National Cancer Institute
NDA	New Drug Application
NGS	National Government Services
NIH	National Institutes of Health
NOA	Notice of Award
NYP	New York-Presbyterian Hospital
NYSPI	New York State Psychiatric Institute
OBA	Office of Biotechnology Activities
OBC	Office of Billing Compliance
OHRP	Office for Human Research Protection
P&S	College of Physicians and Surgeons
PHI	Protected Health Information
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee of the HICCC
PSSV	Pre-Study Site Visit
RCT	Office of Research Compliance and Training
RDRC	Radioactive Drug Research Committee
SAE	Serious Adverse Event
S-I	Sponsor-Investigator
SIV	Site Initiation Visit

SOP	Standard Operating Procedures
SPA	Sponsored Projects Administration
SPF	Sponsored Projects Finance
UP	Unanticipated Problem Involving Risks to Subjects or Others

GLOSSARY OF DEFINED TERMS

Adverse Event (AE): any untoward medical occurrence in a study subject, including any abnormal sign, symptom or disease, temporarily associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

Assent: a child's affirmative agreement to participate in research. Mere failure to object may not, absent affirmative agreement, be construed as assent ([45 CFR 46.402\(b\)](#); [21 CFR 50.3\(n\)](#)).

Biological Product: any virus, therapeutic serum, toxin, anti-toxin, blood, blood component or derivative, allergenic product or analogous microbial product applicable to the prevention, treatment or cure of diseases or injuries. Biological products are derived from living sources, such as humans, animals, plants and microorganisms.

Blinding: a procedure that keeps the type of study intervention unknown to the subject and/or the research team. Also referred to as masking.

Case-Control Study: a retrospective observational study comparing persons without the disease, condition or exposure to compare outcomes between the groups.

Case Report Form (CRF): documentation that records pertinent information on each subject during a clinical trial, based on the protocol.

Child: a person who has not attained the legal age for consent to treatments or procedures involved in the proposed research under the applicable laws of the jurisdiction in which it will be conducted. In New York State, a child is any person under the age of 18 who is not married or a parent ([45 CFR 46.402\(a\)](#); [21 CFR 50.3\(o\)](#)).

Clinical Research Coordinator (CRC): the person who assists an investigator by managing the daily operations of a clinical study in accordance with the protocol, applicable regulations and GCP requirements.

Clinical Research Organization (CRO): a person or entity that assumes, as an independent contractor with the sponsor, one or more obligations of the sponsor.

Clinical Trial Agreement (CTA): a legal contract between the investigator and the sponsor that determines the responsibilities, financial terms, liabilities and proprietary rights relating to a clinical trial.

Cohort: a group of subjects initially identified as having one or more characteristics in common who are followed over time.

Cohort Study: an observational research design where subjects are selected on the basis of an exposure. A cohort study compares the incidence of an outcome in exposed and unexposed groups to help determine whether there is an association.

Control Group: a group of subjects who are not treated with the investigational product and who are used as a comparison to the treatment group.

Covered Entity: an organization that must comply with the HIPAA Privacy Rule, including health care providers and health plans.

Data and Safety Monitoring Committee (DSMC): a panel of experts convened for the purpose of reviewing un-blinded aggregate research data as a means of protecting research participants. The DSMC analyzes comprehensive participation and safety data, reviews the quality of the data and then advises on measures to maintain or improve subject safety throughout the course of a research study. The terms Data and Safety Monitoring Committee and **Data and Safety Monitoring Board (DSMB)** may be used interchangeably.

Data and Safety Monitoring Plan (DSMP): a description of the procedures used to maintain subject safety and data integrity while conducting research. The DSMP may include a prospective plan for assessing subject response, capturing/reporting adverse events, reviewing safety data, monitoring data activities and complying with regulatory requirements.

Data Use Agreement: a written agreement between two entities that specifies how data can be used and shared.

Delegation of Authority Log: a document that identifies the individuals who are authorized by the PI to perform research-related activities. A Delegation of Authority Log contains the names of research team members, the delegated responsibilities and their signatures and/or initials.

Device: an instrument, implement, machine, contrivance, implant, in vitro reagent or other similar or related article, including any component, part or accessory which is intended for use in the diagnosis, cure, treatment or prevention of disease.

Double-Blind: the design of a study in which neither the investigator nor the subjects knows which treatment the subject is receiving.

Drug: an article (other than food) intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease.

FCOI: Financial Conflict of Interest

Form FDA 482: Notice of Inspection: a form completed by a FDA auditor and presented to the most responsible person (e.g., the PI) at the site prior to the start of a FDA inspection.

Form FDA 483: Inspectional Observations: an inspection form completed by a FDA auditor noting deviations, if any, and presented to the most responsible person (e.g., the PI) at the inspected site at the completion of the inspection.

Form FDA 1571: Investigational New Drug Application: a request for FDA authorization to administer an investigational drug to humans. This document provides sufficient data to establish that a drug has demonstrated a reasonable degree of safety and presents a justifiable risk/benefit ratio for testing in humans.

Form FDA 1572: Statement of Investigator: a form required by the FDA for clinical trials involving an Investigational New Drug. This FDA form is signed by the PI responsible for the conduct of the study. It is a statement of responsibilities that designates the PI as responsible for his or her individual conduct as well as the conduct of the IRB and the designated research personnel.

Gene Transfer: the treatment of genetic disease accomplished by altering the genetic structure of either somatic (non-reproductive) or germline (reproductive) cells. Also referred to as gene therapy.

Good Clinical Practice (GCP): the regulations and guidelines that specify the responsibilities of sponsors, investigators, monitors and IRBs involved in clinical research in order to protect the safety, rights and welfare of the subjects as well as ensuring the accuracy of the data collected during the study.

Guardian: an individual who is 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. In New York State, a guardian is any person who (a) is over the age of 18, (b) is a legal resident or citizen of the United States; and (c) has been appointed as a guardian of the person of the child by (i) a parent pursuant to a designation, deed of guardianship or will approved by a Family Court or Surrogate's Court judge; or (ii) a Family Court or Surrogate's Court judge pursuant to a letter or order of guardianship ([45 CFR 46.402\(e\)](#); [21 CFR 50.3\(s\)](#)).

Health Insurance Portability and Accountability Act (HIPAA): federal law passed in 1996 designed to protect the privacy and security of health information. Researchers are required to disclose how research study participation will influence the privacy and security of a subject's protected health information (<http://www.hhs.gov/hipaa/index.html>).

Human Subject (FDA): an individual who is or becomes a participant in research, either as a recipient of a test article or as a control, including, in the case of research involving a medical device, an individual on whose specimen a medical device is used ([21 CFR 50.3\(c\)](#)).

Human Subject (FDA Device Regulations): a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

Human Subject (HHS): an individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual or identifiable private information ([45 CFR 46.102\(f\)](#)).

Identifiable: the identity of the subject is or may readily be ascertained by the investigator or associated with the information ([45 CFR 46.102\(f\)](#)).

Inclusion and Exclusion Criteria: the characteristics that must be present or absent in order for a subject to qualify for a clinical trial, as per the protocol.

Interaction: includes communication or interpersonal contact between investigator and subject ([45 CFR 46.102\(f\)](#)).

Intervention: includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes ([45 CFR 46.102\(f\)](#)).

Investigational Article: a drug (or placebo), a biological product or a medical device being evaluated during a clinical trial.

Investigational Device: a device, including a transitional device, that is the object of an investigation ([21 CFR 812.3\(g\)](#)).

IDE: an Investigational Device exemption.

Investigational Drug: a new drug or biological drug that is used in a clinical investigation ([21 CFR 312.3](#)).

IND: an Investigational New Drug application.

Investigator: an individual who actually conducts a clinical investigation ([21 CFR 50.3\(d\)](#); [21 CFR 312.3](#)).

Investigator's Brochure: a summary of all clinical and non-clinical information known about the investigational product that is relevant to human research: the minimum requirements for its contents are described in the federal regulations.

Investigator-Initiated Research: a research project originating from and administered by an investigator. The research is funded as a result of an investigator submitting an independent research application.

Joint Commission on Accreditation of Healthcare Organizations (Joint Commission): a non-profit, independent organization responsible for inspecting, evaluating and accrediting health care organizations.

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 ([45 CFR 46.102\(r\)](#); [21 CFR 50.3\(e\)](#)).

Limited Data Set: PHI that excludes 16 categories of direct identifiers and may be used or disclosed without obtaining an individual's authorization provided that IRB approval is obtained and a data use agreement is created.

Minimal Risk: the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests ([45 CFR 46.102\(i\)](#); [21 CFR 50.3\(k\)](#)).

New Drug Application (NDA): a comprehensive compilation of the documentation used to support the safety and efficacy of an investigational drug in humans. A new drug application is submitted to the FDA for marketing approval after the conduct of clinical trial(s).

Non-significant Risk Device: an investigational device that does not meet the definition for a significant risk device study as defined by [21 CFR 812](#).

Notice of Grant Award (NGA): the legally binding document that notifies the grantee that an award has been made; contains or references all terms and conditions of the award and documents the obligation of federal funds.

Observational Study: a study design in which subjects are observed for outcomes, but no manipulation or intervention takes place.

Parent: a child's biological or adoptive parent ([45 CFR 46.402\(d\)](#); [21 CFR 50.3\(p\)](#)).

Permission: the agreement of a parent or guardian to the participation of a child in research ([45 CFR 46.402\(c\)](#); [21 CFR 50.3\(r\)](#)).

Placebo: an inactive substance or sham intervention designed to mimic the active intervention. A placebo tries to control for the psychological effects of suggestion.

Privacy Rule: Standards for Privacy of Individually Identifiable Health Information issued pursuant to HIPAA ([45 CFR 160](#); [45 CFR 164](#), [Subparts A and E](#))

Private Information: includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable in order to obtain the information to constitute research involving human subjects ([45 CFR 46.102\(f\)](#)).

Protected Health Information (PHI): information that is created or received by a Covered Entity that relates to the past, present or future physical or mental health or condition of a patient, the provision of health care to a patient, or the past, present or future payment for the provision of health care to a patient, and that identifies the patient or for which there is a reasonable basis to believe that the information can be used to identify the patient.

Protocol: the document that describes the design, objectives, intervention, subject population, methodology, organization and data analysis plan of a research study.

Radioactive Drug: any substance defined as a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons.

Radioisotope: an unstable element that releases radiation as it breaks down. Radioisotopes can be used in imaging tests or as a treatment for cancer.

Radiopharmaceutical: a drug (compound or material) that may be labeled or tagged with a radioisotope. These materials are largely physiological or sub-pharmacological in action, and in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are injected into the body.

Randomization: the process of assigning subjects to study arms using an element of chance to avoid bias.

Research (FDA): an experiment that involves a test article and one or more human subjects that is subject to the IND or IDE regulations or which collects data to be submitted to or held for inspection by the FDA ([21 CFR 50.3\(c\)](#)).

Research (HHS): a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge ([45 CFR 46.102 \(d\)](#)).

Section 404 Research: research not involving greater than minimal risk ([45 CFR 46.404](#); [21 CFR 50.51](#)).

Section 405 Research: research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects ([45 CFR 46.405](#); [21 CFR 50.52](#)).

Section 406 Research: research involving greater than minimal risk and no prospect of direct benefits to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition ([45 CFR 46.406](#); [21 CFR 50.53](#)).

Section 407 Research: research that does not meet the criteria of Section 404, 405 or 406 of Subpart D, but which presents an opportunity to understand, prevent or alleviate a serious problem that affects the health or welfare of children ([45 CFR 46.407](#); [21 CFR 50.54](#)).

Serious Adverse Event (SAE): any adverse event temporarily associated with the subject's participation in research that meets any of the following criteria:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subjects' health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Significant Risk Device: an investigational device that:

- is intended as an implant and presents a potential for serious risk to the health, safety or welfare of a subject;
- is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a subject;
- is for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
- otherwise presents a potential for serious risk to the health, safety or welfare of a subject ([21 CFR 812.3\(m\)](#)).

Source Data: information in original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Source Documents: documents into which Source Data is first entered.

Sponsor: a person or entity that initiates a clinical investigation, but who does not actually conduct the investigation ([21 CFR 50.3\(e\)](#); [21 CFR 312.3](#)).

Sponsor-Investigator (S-I): 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 ([21 CFR 50.3\(f\)](#); [21 CFR 312.3](#)).

Standard Operating Procedures: detailed, written instructions on the performance of a specific function or general operation to achieve consistency and uniformity within an organization.

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 sections 351 and 354-360F of the U.S. Public Health Service Act ([42 USC 262 and 263b – 263n](#)) ([21 CFR 50.3\(j\)](#)).

Triple Blind: a study design in which the investigators, the subjects and the individuals who organize and analyze the data do not know if the intervention or control is being used.

Unanticipated Adverse Device Effect (UADE): 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...or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Unanticipated Problem (UP): any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Un-blinded: a study design in which investigators, subjects and the individuals who organize and analyze the data know the treatment assignment.

Ward: any child who is under the protection of the state or any other agency, institution or entity. In New York State, any foster child should be considered a ward for purposes of [45 CFR 46, Subpart D](#). A foster child is any child in the care, custody or guardianship of an authorized agency, who is placed for temporary or long term care.

Washout: a period during which subjects are taken off a previous treatment to eliminate the biological effects of the substance.

NYP AFFILIATES

Divisions

New York-Presbyterian Hospital/Columbia University Medical Center

New York-Presbyterian/Weill Cornell Medical Center

New York-Presbyterian/The Allen Hospital

New York-Presbyterian/Lower Manhattan Hospital

New York-Presbyterian/Westchester Division

Regional Hospital Network

New York-Presbyterian/Hudson Valley Hospital

New York-Presbyterian/Lawrence Hospital

New York-Presbyterian/Queens

NYP CLINICAL TRIAL BILLING PROCEDURES

A. Outpatient Billing

The following steps should be followed for billing relating to any clinical trial that involves the use of NYP outpatient ancillary services that will be paid from the research budget:

Step 1: Obtain a Financial Class Number (FCN)

For non-industry sponsored trials, the CRC should provide the protocol, an IRB Certificate and a list of NYP ancillary services that the study will require to the Budget Analyst in the CTO assigned to the study. For industry sponsored trials, the CTO already has this information. In either case, the Budget Analyst will request the FCN from the NYP General Accounting Department (current contact: Verona Sinclair at sinclair@nyp.org). The NYP instruction sheet (Outpatient Hospital Ancillary Billing Procedure for Clinical Trial studies (Blue Bill Charges)) and a sample Research Study Financial Class Request Form can be found at the end of this Annex D.

Once set up, the FCN will be forwarded by the NYP General Accounting Department to the PI, the CRC and the DA via email. CRCs should allow two weeks from the time of submitting the request to NYP to schedule patient appointments for hospital services. A patient cannot be registered into a Financial Class prior to the “production date” (i.e., the date designated by the NYP General Accounting Department as the first day that the FCN is active).

Be sure that an IRB renewal certificate is sent to the NYP General Accounting Department (current contact: Verona Sinclair at sinclair@nyp.org) on an annual basis to ensure that the FCN will not be closed.

Step 2: Obtain a Patient Serial Number (PSN)

In order to obtain a PSN, the CRC should fill out a Research Patient Registration Request Form and send it to the NYP Access Unit by fax (212) 491-2344 or email at opgrantreg@nyp.org with the following information:

- The FCN assigned to the study
- Last and first name of the patient
- Patient’s Date of Birth and NYP Medical Record Number (MRN).

The assigned PSN will be returned to the CRC via fax or email. A sample Research Patient Registration Request Form can be found at the end of this Annex D.

Step 3: Fill out a Red Grant Requisition Form (GRF)

When the patient is sent for any study-related ancillary service at NYP, the CRC should fill out a GRF for research (not standard of care) billing, which is a red and white 8" X 3.5" NCR form. CRCs should write the FCN and PSN on each GRF. CRCs should retain a copy of the GRF for the study records. A sample GRF can be found at the end of this Annex D.

Please note that the GRF can be used only for services billed to the research study. If the patient is receiving both standard of care and study related services, both a GRF and a standard Lab or Ancillary Procedure Requisition Form should be used. The GRF is typically sent with the patient to the ancillary service to be delivered to a representative of the department where the ancillary service is located.

Step 4: Review the Blue Bill

A NYP invoice – called the Blue Bill – for ancillary services is sent to the applicable CRC or DA on a monthly basis. An “OP Billing Calculation Posting Journal” report is attached to the Blue Bill, which lists the services rendered and the amount charged for each. The CRC should review the Blue Bill to confirm that the services were rendered and the invoice is correct. If the Blue Bill is correct, the CRC or DA should write the billing directions on the Blue Bill and return it to the NYP General Accounting Department (current contact: Verona Sinclair at sinclair@nyp.org). If the charges are not correct, circle the amount(s) not to be paid and write “not part of study” and fax the changes to the NYP General Accounting Department.

B. Inpatient Billing

If the research study involves inpatient admissions, the NYPresbyterian Inpatient Research Study Information Sheet must be completed and returned to the NYP General Accounting Department. If the admission is a non-Clinical Research Resource (**CRR**) admission, an Admission Information Sheet-Research Patients must be completed and faxed to the Manager of Milstein Admitting (adults) or the Director of MSCHONY (pediatric/maternity). (If the patient is to be admitted to the Irving Institute’s CRR, the Institute will have additional admission forms.) The NYP instruction sheet (Inpatient Research Study Billing Procedures) and a sample Inpatient Research Study Information Sheet can be found at the end of this Annex D.

SAMPLE



Outpatient Hospital Ancillary Billing Procedure For Clinical Trial Studies (Blue Bill Charges)

Here is an outline to follow for research studies that involve *outpatient* ancillary services that should be paid for by the study's funding. If the study also involves inpatient, please follow I/P procedure too.

When the Study Agreement has been signed and fully executed for *industry sponsored trials* through the Clinical Trials Office, the budget analyst working on that study (342-3956) will proceed with setting up a financial class number as soon as the study has been assigned CU Acct #. If the study is NIH, please advise the Budgets group and provide protocol, IRB certificate and list of labs /procedures in order to send the financial class form to the General Accounting Department. The account information will be forwarded to the P.I., study coordinator and the departmental administrator via email by Verona Sinclair (Gen Acctg Dept). Please allow two weeks from time of execution to make appointments for patients to come in for hospital services. A patient cannot be registered onto the financial class number until the production date.

The Research Coordinator must submit a list of patients to be enrolled on the financial class number. This list should go to: Office Fax Number: 212 491-2344

For emergencies: Carol Caraway 305-6381, work cell is 212-491-2341 and email is cac9005@nyp.org

Send e-mail to opgrantreg@nyp.org

Please include on the list:

- ❖ The Financial Class number
- ❖ Last, First name of each patient
- ❖ Patient's DOB & Medical Record number

A serial number will be assigned to the patient whom in turn you should use on the grant requisition slips when sending patients for labs/procedures. When you send a patient for an ancillary service in the hospital, use the grant requisition form and hand write the patient's serial number. Try to keep a copy of the requisitions for your records. Do not use the regular laboratory requisitions. All study paid services must be on a grant slip. A serial number is patient specific and is the internal link in the hospital billing system from the patient to a specific financial class number

On a monthly basis the Administrator of your department will receive the blue bill invoice (your 67 account). In turn he/she should send the "**OP Billing Calculation Posting Journal**" report, which is attached to the invoice, to the P.I. or research coordinator for review and approval of payment. On the report you will see under the financial class number, the patient's name, date and description of service and amount charged (actual amount charged is in the third column). Once the report has been reviewed, send it back to the Administrator with the approved amount for payment. If you see charges for patients that don't belong to the study, please *neatly* circle amount not to be paid and write "not part of study". Fax the pages with the incorrect charges back to Verona Sinclair at sinclair@nyp.org the patient/insurance will be billed for those charges and your account will be credited.

Any additional questions regarding billing please can be directed to:

Verona Sinclair
Accountant,
General Accounting Office
212-585-6553
sinclair@nyp.org

You will receive separate invoices for professional fees and procedures on university equipment from the University departments when applicable.

SAMPLE

RESEARCH STUDY FINANCIAL CLASS REQUEST FORM - NY PRESBYTERIAN O/P ANCILLARY SERVICES

Please include approved budget & protocol when submitting this form

DATE _____ REQUESTED BY _____

SPONSOR _____ DEPARTMENT/DIV. _____

STUDY NAME _____

PRINCIPAL INVESTIGATOR (incl phone#&email) _____

RESEARCH COORDINATOR (incl phone#&email) _____

FINANCIAL ADMINISTRATOR (incl phone#&email) _____

STUDY START DATE _____

Is this study being administered by:

STUDY END DATE _____

please circle one

CU ACCT# _____

Grants & Contracts or Clinical Trials

BLUE BILL # _____

Rascal # _____ IRB# _____

BUDGET ALLOCATED FOR ANCILLARY CHARGES:

Year 1	\$		Year 3	\$		Year 5	\$	
Year 2	\$		Year 4	\$		Year 6	\$	

OUT PATIENT INFORMATION - If this research trial involves a hospital admission please use the inpatient information form.

1) How many patients expected to be enrolled? _____

3) What location will patients be sent to? _____

2) What ancillary services is the study paying for? _____

A) Specify how many times each test will be performed on pt _____

B) Please include CPT codes or Charge Code _____

FC _____ (to be assigned by NYP Hospital General Accounting Department)
--

Blue Bill accounts for Research will be set up by Accounting office. Please include Blue Bill request form if a new account is needed.
 if you have any questions

--	--	--	--	--	--	--	--	--	--

SEND COMPLETED FORM TO:
 Senior Accountant (Verona Sinclair)
 General Accounting Department
 Fax Number 212-297-5988

as of 2/1/10

SAMPLE



RESEARCH PATIENT REGISTRATION REQUEST FORM

To: Access Unit	From:
Address: 534 W.135 th St.	Department:
E-mail: Carol Caraway cac9005@nyp.org , Maria Contrerascontrem@nyp.org, Taressa Kears 9015@nyp.org	Phone:
Fax: 212-491-2344	Fax:

PLEASE REGISTER THE FOLLOWING PATIENTS TO FC#

Last Name	First Name	Medical Record #	Date of Birth	Serial # (completed by central registration)

Date Faxed:	Date Completed:
--------------------	------------------------

SAMPLE

RED GRANT REQUISITION REQUIRED FIELDS

- 1 Eagle Financial Class – (Financial Class Code)**
 - Three character code used to identify a specific grant. Most grant financial classes are numeric codes.
- 2 Medical Record Number**
 - Seven digit hospital specific number associated with each individual patient.
- 3 Location of Physician**
 - Describe the Department for the physician (e.g. Neurology, Cardiology, Dermatology). [Required by Lab Dept]
- 4 Patient Name**
 - The patient's name written Last name, First name & Middle Initial.
- 5 Diagnosis Code**
 - ICD-9 Code used for this patient.
- 6 Date of Birth - Patient's date of birth (MM/DD/YYYY).**
- 7 Eagle Account Number (Patient Serial Number)**
 - Eight digit Code -For Grant registrations, the Eagle Account Number always begins with a "7" (e.g. 77777770).
- 8 Doctors Name - Referring Physician.**
- 9 Contact Telephone number**
 - *Grant Coordinator's Phone number – not MD!*
- 10 Exam Requested**
 - Name of Exam requested – if using the Long Lab Request form be sure to include the 'Eagle Acct. Number' on the form.
- 11 Clinical Information**
 - "For Clinical Trial Procedure" should be written here.

Draft

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SAMPLE

INPATIENT RESEARCH STUDY BILLING PROCEDURE

When implementing a research study that involves inpatient admission, the **NY Presbyterian Inpatient Research Study Information Sheet** *must be completed* and returned to the **General Accounting Department** along with the study's budget and protocol.

If the admission is a non-CRR admission you will need to complete the **admission information sheet-research patients** and fax it to the **Manager of Milstein Admitting** (adults) or **The Director of MSCHONY** (peds/maternity). CRR admissions will be handled by the Irving Center via their admitting forms.

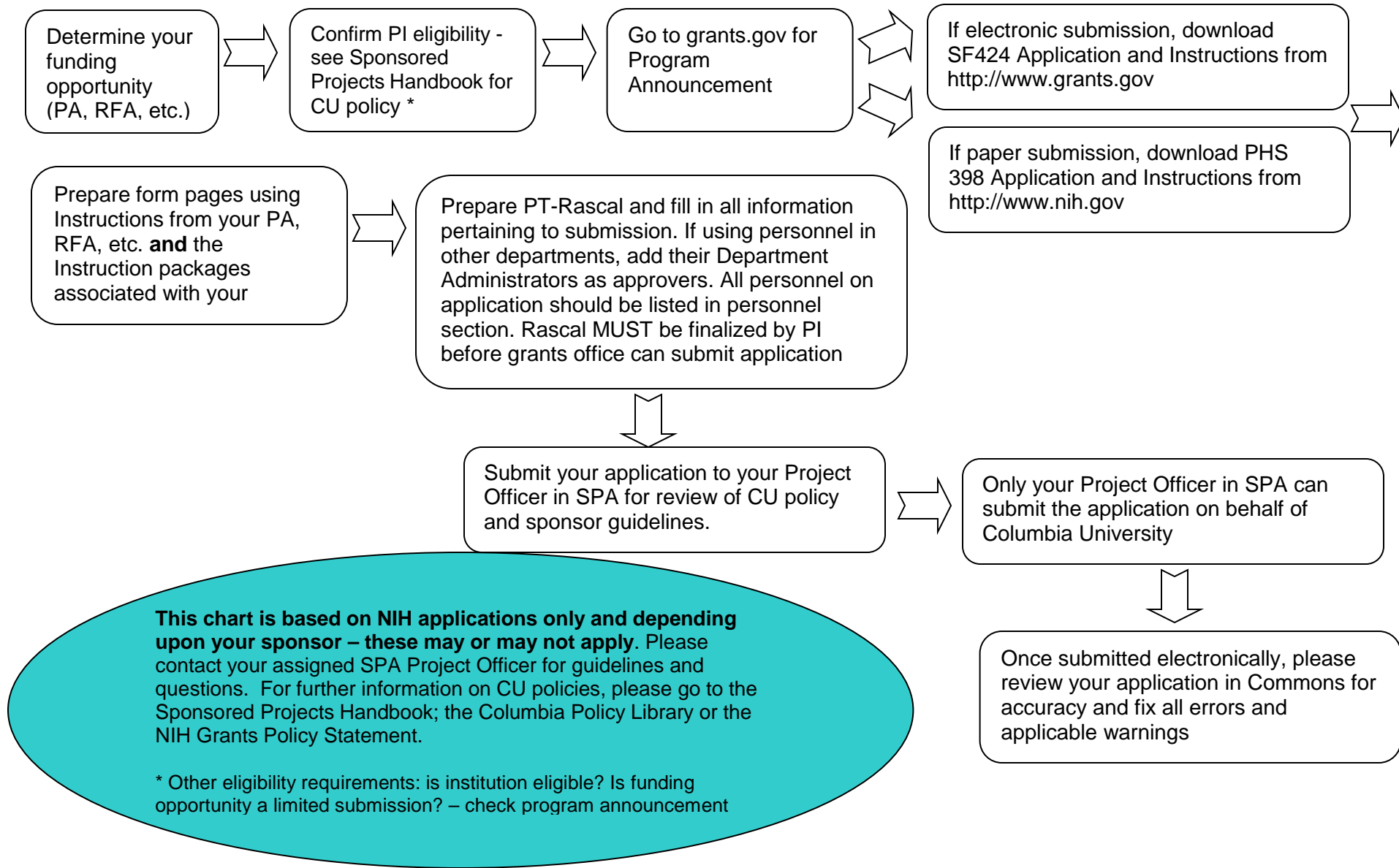
1. A-Day (CRC –G10) – Entire admission is covered by the CRR (including the ancillaries).
 - ❖ Complete inpatient research study information sheet
2. A-Day (CRC-G13) – Room & board is covered by CRR, ancillaries (RCC rate of chargemaster cost) will be billed to the P.I. for payment. The P.I. will receive a patient bill with the ancillaries listed.
 - ❖ Complete inpatient research study information sheet. Guarantor Information must be completed.
3. B-Day (Insurance Code)– Admission is split between insurance coverage and CRR.
 - ❖ Complete inpatient research study information sheet.
4. **B-Day (Non-CRC –Insurance Code) – Entire admission is covered by insurance but specific tests will be billed to the study through a blue bill account.**
 - ❖ **Complete Inpatient Research Study Information Sheet**
 - ❖ **Complete Research Study Financial Class Request form**
 - ❖ **Complete Admission Information Sheet-Research Patients**
 - ❖ **Complete Research Patient Registration Request form prior to services**
 - ❖ **Include Patients' Serial #s on Charge Requisition form for specific study test**
5. D-Day (CRC-R10) – Admission is in the CRR but the entire stay is paid for by the P.I. These are industry sponsored studies. The per diem charge includes all ancillaries. The P.I. will receive a patient bill.
 - ❖ Complete Inpatient Research Study Information Sheet
6. D-Day (Non-CRC-R10) – This is an industry sponsored study with patients being admitted in any unit other than the CRR. The per diem charge includes all ancillaries. The P.I. will receive the patient bill.
 - ❖ Complete Inpatient Research Study Information Sheet
 - ❖ Complete Admission Information Sheet-Research Patients

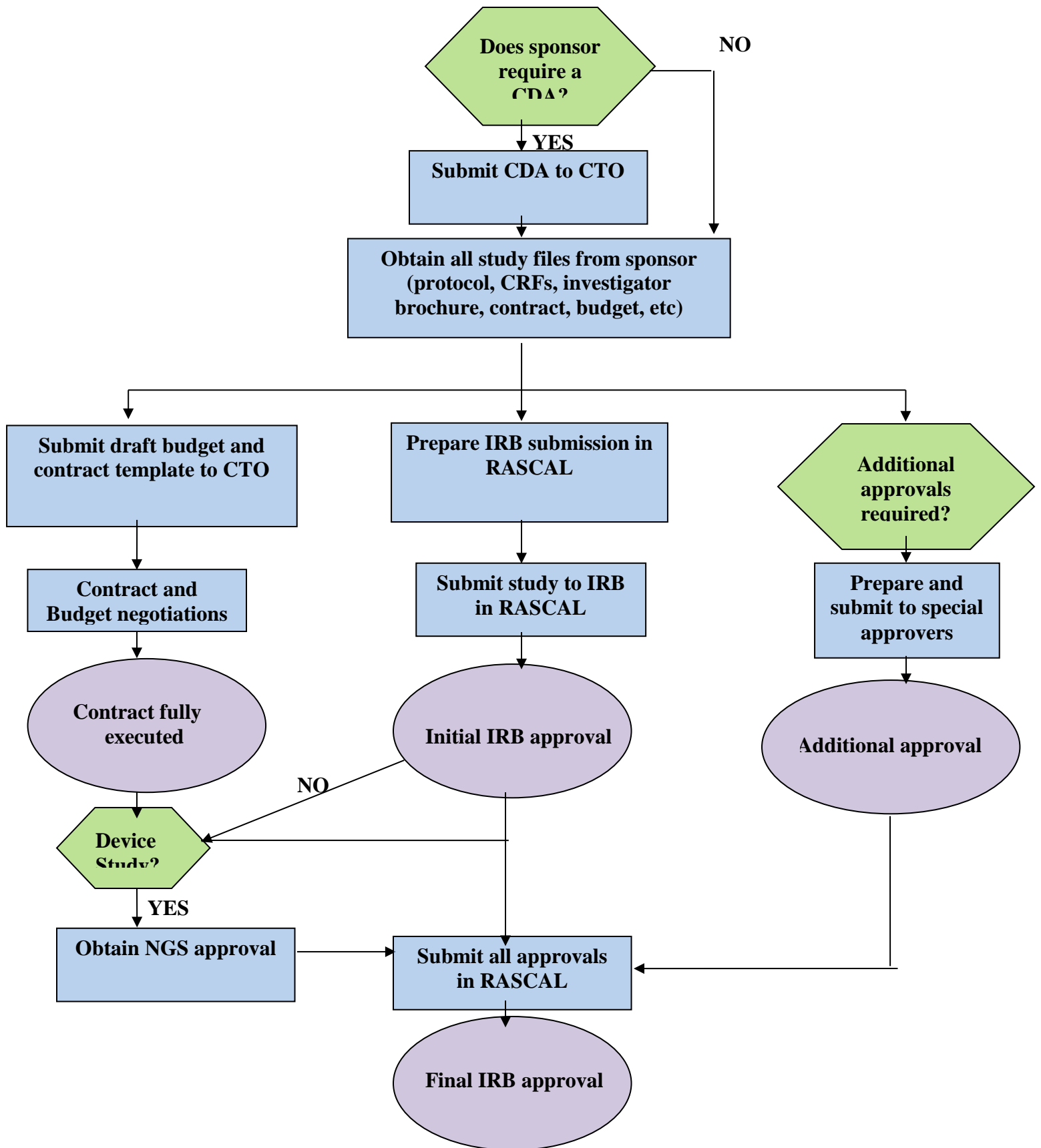
If the study also includes the patient coming to the hospital for outpatient ancillary services, the Research Study Financial Class Request Form will be completed by the Clinical Trials Office.

SAMPLE

NY PRESBYTERIAN INPATIENT RESEARCH STUDY INFORMATION SHEET		Date: _____	
Department/Division			
Study Name			
Sponsor			
Principal Investigator (incl phone# & email)			
Research Coordinator (incl phone# & email)			
Financial Administrator (incl phone# & email)			
CU ACCT #		Study Start Date:	
Is this study being administered by: please circle one		Study End Date:	
Grants & Contracts or Clinical Trials		Rascal #	IRB #
<i>NOTE: Please include approved budget, consent form & IRB letter when submitting this form</i>			
IN PATIENT INFORMATION			
1) What portion of the admission is being covered by the study?			
Please check appropriate answer		Yes	No
		If answer is Yes, How many days?	
a) Entire Admission - (D-day)			# of days
b) Partial Admission			
- some days are paid by insurance			# of days
- some days are paid by GCRC (A-days)			# of days
- some days are paid by the study (D-days)			# of days
c) Admission is paid by insurance but a specific procedure or test will be done (paid by study)			FC#
d) Admission is paid by GCRC but some or all ancillaries will be paid by study			
<i>NOTE: You will also need to submit the Research Study Financial Class Request Form if c) is yes</i>			
2) Where will patients be admitted to?		3) How many admissions/pt?	
4) Please specify what the test(s) and/or procedures(s) are and how many times it will be done per admission:			
Test/Procedure	# of Times	Test/Procedure	# of Times
1)		5)	
2)		6)	
3)		7)	
4)		8)	
Guarantor Information			
This information is needed to ensure that the billing of D-days and ancillaries for GCRC admissions are sent to the correct Principle Investigator.			
Principal Investigator's Name: _____			
Location of Office in Hospital: _____			
Phone Number _____			
If you have any questions regarding the inpatient billing process, please call Verona Sinclair, 585-6553 or email at sinclair@nyp.org			
SEND COMPLETED FORM TO:			
Verona Sinclair			
General Accounting			
Fax Number 212-297-5988			
			as of 5/20/04

FLOWCHARTS FOR SPONSORED CLINICAL RESEARCH





FORMS AND LOGS

SAMPLE BUDGET WORKSHEET

PI - Dr. XYZ

Total

Study Name / IRB protocol #	Baseline Visit	Procedure Visit	Pre- Discharge Visit	1 Month Visit	6 Month Visit	12 Month Visit	2 Year Visit	3 Year Visit	Completion of Study/Close Out Activities	
Examination/History/Documentation/Logistics										
Medical History/Physical Examination	NB									
Procedure Information		NB								
NIH Stroke Scale Examination	SOC		SOC	SOC	SOC	SOC	SOC	SOC		
Document Adverse Events		NB	NB	NB	NB	NB	NB	NB		
Document Interventions		NB	NB	NB	NB	NB	NB	NB		
Document Concomitant Medication	NB	NB	NB	NB	NB	NB	NB	NB		
Discontinuation Information		NB	NB	NB	NB	NB	NB	NB		
CRF Form	GR	GR	GR	GR	GR	GR	GR	GR		
Completion of all study related tasks and paperwork									NB	
Principal Investigator Fees	GR	GR	GR	GR	GR	GR	GR	GR	GR	
Study Coordinator Fees	GR	GR	GR	GR	GR	GR	GR	GR	GR	
Subtotal Examination/History/Documentation/Logistics										
Ancillaries										
Carotid angiography	SOC									
Serum Creatinine	SOC									
Cardiac Enzymes (CK, CKMB, or Troponin)	SOC		SOC							
CBC	SOC		SOC							
Platelet Count	SOC									
Urine Pregnancy test	SOC									
12 lead ECG	SOC		SOC	GR						
Carotid Duplex Ultrasound	SOC		SOC	SOC	SOC	SOC	SOC	SOC		
CT or MRI	SOC		SOC	SOC	GR	SOC	SOC	GR		
Subtotal Ancillaries										
Professional Reading/Interpretation Fees										
Carotid Duplex Ultrasound Reading Fee	SOC		SOC	SOC	SOC	SOC	SOC	SOC		
Video Tape and Dubing of Taping	GR	GR	GR	GR	GR	GR	GR	GR		

SOC = Bill Insurance

GR = Bill Study Account/Sponsor

NB = No Billing

Note: Study device is category B and billable to insurance. Price

Protocol Name

SAMPLE CASE REPORT FORM

Subject ID: _____

Visit Date: _____
m m d d y y y y
Visit: Enrollment Week 1 Month 1 Month 6 Month 12

Instructions: Complete this form for each required study visit, whether it was kept or missed. For missed visits, record the last date of the visit window in the header.

1. Was the subject seen for the study visit? Yes (***skip to question # 3***)
 No

2. Indicate the reason for the missed study visit.
 (Check only one) Unable to locate or contact
 Refused participation or withdrew consent
 Illness
 Death (***Complete AE log & Off-Study Form***)
 Other, specify: _____

3. Vitals Collected

Height: _____ <input type="checkbox"/> cm <input type="checkbox"/> Not Done <input type="checkbox"/> in	Weight: _____ <input type="checkbox"/> kg <input type="checkbox"/> Not Done <input type="checkbox"/> lb	Blood Pressure: _____ / _____ <input type="checkbox"/> Not Done Systolic(mm Hg) / Diastolic(mmHg)
Pulse Rate: _____ <input type="checkbox"/> Not Done	Respiration Rate: _____ <input type="checkbox"/> Not Done	Temperature: _____ °C <input type="checkbox"/> Not Done <input type="checkbox"/> F

4. Did the subject receive study drug? Yes
 No
 Not Applicable

5. Did the subject have any Adverse Events since the last visit? Yes (***Complete AE Log***)
 No

Comments: _____

Signature: _____ Date: _____

Sample Delegation of Authority Log

Protocol: _____	IRB#: _____
Principal Investigator: _____	Site: _____

Although as Principal Investigator I remain responsible for the proper conduct of the study, I hereby authorize the following co-Investigators and members of the participating institution's staff to perform the tasks assigned to him/her. I affirm that each member of the participating institution staff listed below will be trained and qualified prior to performing the task(s) delegated.

Each person indicated below, by signing, agrees to comply with the study protocol and the applicable regulations for the study when performing his/her assigned task(s).

Authorized Personnel			Task(s) ¹	Task(s) Start Date	PI Initials & Date	Task End Date ²	PI Initials & Date ²
Printed or Typed Name	Signature	Initials					

- ¹ Complete the number(s) corresponding to the task(s) being delegated.
- | | | |
|-----------------------------------|--|---|
| 1. Informed Consent Process | 6. Blood Draw | 10. CRF(s) Data Correction after sign-off |
| 2. Subject Eligibility Assessment | 7. Vitals | 11. All Tasks (1-10) |
| 3. CRF(s) Sign-off | 8. Adverse Events Assessment | 12. Blood/Sample Storage and Shipment |
| 4. Physical Exam | 9. Completion/Correction of CRF(s) prior to sign-off | 13. Staff Training |
| 5. Mental Status Assessment | | 14. Other |
- ² Update as personnel leave and/or assigned task(s)

Principal Investigator Signature (at study closure): _____ Date: _____

Sample Screening / Enrollment Log

Principal Investigator: _____ Study Title: _____ IRB Number _____

Patient Initials	Date of Birth	Date of Consent	Patient ID Number	Randomized YES/NO	If NO, Reason not Enrolled	If YES, Treatment Group 1, 2, or 3*

The purpose of this document is to aid in enrollment and understand enrollment patterns.

Directions for use:

1. Enter all patients screened for the study.
2. Assign Patient ID numbers in a sequential manner to patients who sign informed consent.
3. For patients not randomized, include the reason patient failed to be enrolled.

*This column may not be applicable to many types of studies, including blinded randomized trials.

Protocol Name

SAMPLE INCLUSION AND EXCLUSION CRITERIA CHECKLIST

ID # | | | | |

DATE: | | | | | | | | | | | | | | | |
m m d d y y y y

Visit Type: [] Screening [] Baseline

Staff Initials: | | | | |

Inclusion Criteria

- 1. Is the subject a female between the ages of 18-65? [] Yes [] No
2. Does the subject suffer from migraines? [] Yes [] No
3. Is the subject willing to use effective contraception throughout the period of study drug administration? [] Yes [] No
4. Is the subject willing to return for follow-up visits every 3 months for the length of the study, which is 2 years? [] Yes [] No
5. Is the subject able to provide informed consent? [] Yes [] No

Exclusion Criteria

- 6. Does the subject have a known allergy to penicillin? [] Yes [] No
7. Does the subject have a white blood cell count of less than 3.5/mm3? [] Yes [] No
White blood cell count: _____ mm3 Date: _____
8. Does the subject have a platelet count less than 100,000/mm3 at visit? [] Yes [] No
Platelet count: _____ mm3 Date: _____
9. Has the subject suffered any head trauma within the last 6 months? [] Yes [] No
10. Is the subject currently pregnant? [] Yes [] No

Subject is eligible for the study if all the INCLUSION criteria are YES and all the EXCLUSION criteria are NO.

- 11. Does the subject meet the eligibility requirements for this study? [] Yes [] No

Investigator's Statement Concerning Eligibility

I have verified the data entered in the Case Report Form and have determined that it is complete, accurate and compatible with the source documents.

Investigator's Printed Name

Investigator's Signature

Date

Sample Specimen Shipping Log

Date	Patient number	Accession number (lab)	Frozen or ambient?	Shipping method	Tracking number	Comments
4/1/04	162-001	Bl 04-132	Ambient	Speed-R-US	01984	Hemolyzed due to delay in shipping

Protocol number _____

Site number _____

Sample Device Accountability Log

Study Title:
 IRB#:
 Name of Device:
 Principal Investigator:
 Site Name and Number:

Date Device Received	Model Number	Serial Number	Expiration Date	Date Device Used	Subject Study Number	Final Disposition	Date of Final Disposition	Reason for Final Disposition

Principal Investigator

Sample Adverse Events Log

Protocol: _____

IRB#: _____

Principal Investigator: _____

Site: _____

Subject ID#	Adverse Event (Please use medical terminology)	Serious Adverse Event	Start Date	End Date -OR- Continuing	Severity (grade)	Relatedness to Drug	Outcome	Report to IRB and/or FDA (if applicable)	PI Initial & Date
		<input type="checkbox"/> No <input type="checkbox"/> Yes * <small>*Complete SAE Form</small>	____/____/20____ <small>(mm/dd/yyyy)</small>	____/____/20____ <small>(mm/dd/yyyy)</small> <input type="checkbox"/> Continuing	<input type="checkbox"/> 1 - Mild <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 4 - Life Threatening <input type="checkbox"/> 5 - Death	<input type="checkbox"/> Definitely <input type="checkbox"/> Probably <input type="checkbox"/> Possibly <input type="checkbox"/> Unlikely <input type="checkbox"/> Not Related <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered/Resolved without Sequelae <input type="checkbox"/> Recovered/Resolved with Sequelae <input type="checkbox"/> Recovering/resolving <input type="checkbox"/> Intervention for A/E continues <input type="checkbox"/> Not resolved/not recovered <input type="checkbox"/> Other <input type="checkbox"/> Resolved	IRB <input type="checkbox"/> Yes <input type="checkbox"/> No FDA <input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> No <input type="checkbox"/> Yes * <small>*Complete SAE Form</small>	____/____/20____ <small>(mm/dd/yyyy)</small>	____/____/20____ <small>(mm/dd/yyyy)</small> <input type="checkbox"/> Continuing	<input type="checkbox"/> 1 - Mild <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 4 - Life Threatening <input type="checkbox"/> 5 - Death	<input type="checkbox"/> Definitely <input type="checkbox"/> Probably <input type="checkbox"/> Possibly <input type="checkbox"/> Unlikely <input type="checkbox"/> Not Related <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered/Resolved without Sequelae <input type="checkbox"/> Recovered/Resolved with Sequelae <input type="checkbox"/> Recovering/resolving <input type="checkbox"/> Intervention for A/E continues <input type="checkbox"/> Not resolved/not recovered <input type="checkbox"/> Other <input type="checkbox"/> Resolved	IRB <input type="checkbox"/> Yes <input type="checkbox"/> No FDA <input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> No <input type="checkbox"/> Yes * <small>*Complete SAE Form</small>	____/____/20____ <small>(mm/dd/yyyy)</small>	____/____/20____ <small>(mm/dd/yyyy)</small> <input type="checkbox"/> Continuing	<input type="checkbox"/> 1 - Mild <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 4 - Life Threatening <input type="checkbox"/> 5 - Death	<input type="checkbox"/> Definitely <input type="checkbox"/> Probably <input type="checkbox"/> Possibly <input type="checkbox"/> Unlikely <input type="checkbox"/> Not Related <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered/Resolved without Sequelae <input type="checkbox"/> Recovered/Resolved with Sequelae <input type="checkbox"/> Recovering/resolving <input type="checkbox"/> Intervention for A/E continues <input type="checkbox"/> Not resolved/not recovered <input type="checkbox"/> Other <input type="checkbox"/> Resolved	IRB <input type="checkbox"/> Yes <input type="checkbox"/> No FDA <input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> No <input type="checkbox"/> Yes * <small>*Complete SAE Form</small>	____/____/20____ <small>(mm/dd/yyyy)</small>	____/____/20____ <small>(mm/dd/yyyy)</small> <input type="checkbox"/> Continuing	<input type="checkbox"/> 1 - Mild <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 4 - Life Threatening <input type="checkbox"/> 5 - Death	<input type="checkbox"/> Definitely <input type="checkbox"/> Probably <input type="checkbox"/> Possibly <input type="checkbox"/> Unlikely <input type="checkbox"/> Not Related <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered/Resolved without Sequelae <input type="checkbox"/> Recovered/Resolved with Sequelae <input type="checkbox"/> Recovering/resolving <input type="checkbox"/> Intervention for A/E continues <input type="checkbox"/> Not resolved/not recovered <input type="checkbox"/> Other <input type="checkbox"/> Resolved	IRB <input type="checkbox"/> Yes <input type="checkbox"/> No FDA <input type="checkbox"/> Yes <input type="checkbox"/> No	
		<input type="checkbox"/> No <input type="checkbox"/> Yes * <small>*Complete SAE Form</small>	____/____/20____ <small>(mm/dd/yyyy)</small>	____/____/20____ <small>(mm/dd/yyyy)</small> <input type="checkbox"/> Continuing	<input type="checkbox"/> 1 - Mild <input type="checkbox"/> 2 - Moderate <input type="checkbox"/> 3 - Severe <input type="checkbox"/> 4 - Life Threatening <input type="checkbox"/> 5 - Death	<input type="checkbox"/> Definitely <input type="checkbox"/> Probably <input type="checkbox"/> Possibly <input type="checkbox"/> Unlikely <input type="checkbox"/> Not Related <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered/Resolved without Sequelae <input type="checkbox"/> Recovered/Resolved with Sequelae <input type="checkbox"/> Recovering/resolving <input type="checkbox"/> Intervention for A/E continues <input type="checkbox"/> Not resolved/not recovered <input type="checkbox"/> Other <input type="checkbox"/> Resolved	IRB <input type="checkbox"/> Yes <input type="checkbox"/> No FDA <input type="checkbox"/> Yes <input type="checkbox"/> No	

Principal Investigator Signature: _____

Date: _____

Page ____ of ____

Sample Serious Adverse Event Report

Study title: _____ Protocol number: _____

Patient initials: _____ Subject number: _____

Nature of Event

For example, myocardial infarction

Description of Event

- | | |
|---|---|
| <input type="checkbox"/> Death | <input type="checkbox"/> Life-threatening |
| <input type="checkbox"/> Resulted in or prolonged hospitalization | <input type="checkbox"/> Disabling |
| <input type="checkbox"/> Birth defect | |

Was the event unexpected? Yes No
("Unexpected" means that the event was not previously described in the Investigator's Brochure, protocol, or consent)

Brief Narrative

Describe the onset, treatment, and clinical course of the SAE so far.

Admission date: _____ Discharge date post-SAE: _____

Sample Serious Adverse Event Report, Cont'd

Secondary Suspect/Concomitant Therapy Information

Drug name	Daily dosage	Start date	Stop date	Indication for use	Causally related?

Laboratory Results

Please record the results below, including normal and/or abnormal results of all laboratory and diagnostic tests relevant to the SAE, or attach the results.

Date	Test	Result	Comment

Causality

In your opinion, how likely do you believe that this adverse event was related to the study drug or device?

- | | |
|---|--|
| <input type="checkbox"/> Definitely related
<input type="checkbox"/> Possibly related (maybe)
<input type="checkbox"/> Definitely not related | <input type="checkbox"/> Probably related (likely)
<input type="checkbox"/> Probably not related (unlikely)
<input type="checkbox"/> Can't judge |
|---|--|

Contacts for Additional Information

Name of responsible or reporting physician:

Signature of responsible or reporting physician:

Phone: _____ Fax: _____