

Guidelines for the Conduct of Clinical Research Activities

At

Montefiore Medical Center and its Affiliates

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INTRODUCTION

This document is provided as institutional guidelines for the conduct of Clinical Research Activity at Montefiore Medical Center (MMC) and its affiliates. The aim of these guidelines is to standardize and simplify organization and documentation relating to clinical research, thereby fostering conformance to Good Clinical Practice (GCP) requirements within clinical research at MMC and its affiliates, and in accordance with institutional policies and procedures. The templates provided within, if implemented, will permit a useful degree of uniformity in the performance of said research at the institution.

These guidelines are intended for MMC and affiliated staff involved with conducting clinical research, including but not limited to investigators, research nurses, study coordinators, data managers and research administrators. All personnel involved in the conduct of clinical research at MMC or any of its affiliates should refer and adhere to these guidelines in their research practice. These guidelines are subject to all applicable federal laws and regulations, i.e. HHS, FDA, HIPAA. Should any conflicts between federal laws or regulations and such guidelines arise, said laws and regulations shall overrule.

These guidelines constitute a living document and are subject to change by the Institution. Major changes to these guidelines shall be communicated to clinical research personnel. Clinical research personnel should be familiar with these guidelines and any changes therein.

Good Clinical Practice (GCP)

Montefiore Medical Center (MMC) and its affiliates adhere to the principles of Good Clinical Practice (GCP) established by the International Conference on Harmonization (ICH) for all human subject-related research. Effective as of January 1, 2015, all personnel involved in clinical research at MMC and/or its affiliates must have certification of completion of GCP Training prior to conducting any clinical research activity. This is applicable to investigations of FDA regulated clinical trials using human subjects conducted, in whole or in part, by or under the supervision of MMC faculty, staff or students, or utilizing MMC facilities, funding or other institutional resources and/or those of its affiliates.

WHAT IS CLINICAL RESEARCH?

Clinical research is medical research that directly involves or that uses materials from humans, such as their behavior or samples of their tissue. The research may involve a specific individual or groups of people (also called subjects), and aims to uncover better ways to treat, prevent, diagnose, and understand human disease. Clinical research is conducted according to a plan known as a *protocol*, which is designed to safeguard the participants' health and answer specific research questions.

Types of Clinical Research

Clinical Research can be subdivided into two major groups according to research design: *observational studies* and *clinical trials*. In observational studies, investigators assess health outcomes in groups of participants in accordance with the research protocol. Any intervention performed on participants of observational studies (including medical products, such as drugs or devices, or procedures) is done so as part of their routine medical care. Participants are not assigned to specific interventions by the investigator, and there is no attempt at intervention or at altering the course of the disease.

Clinical trials (also called *interventional studies*) involve participants who may receive experimental medical interventions in the form of medical procedures, drugs, or devices. The investigator observes the effects of the experimental intervention in a controlled environment. Participants of clinical trial studies are assigned or *randomized* into different treatment groups in an attempt to control for investigator bias. Clinical trials may compare a new medical approach to an available standard of care or to a placebo containing no active ingredients, or to no intervention at all. Additionally, some trials compare available interventions to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or better than an existing and available treatment alternatives (including no intervention). Clinical trial investigators try to determine the safety and efficacy of the intervention by measuring specific outcomes in the participants.

There are various types of clinical research that take place at Montefiore Medical Center and its affiliates. The following paragraphs describe the most common forms of clinical research taking place at the institution.

Observational Studies

Cohort Studies

Cohort studies are longitudinal studies that consist of one or more participant groups (called *cohorts*) that are followed prospectively and monitored via subsequent status evaluations with respect to a disease or outcome. Cohort studies are conducted to determine which initial participants' exposure characteristics (risk factors) are associated with said disease or outcome. Participant outcome is measured throughout the life of the study, and relationships with specific characteristics are determined. An example of a cohort study is the *patient registry*.

Patient Registries

A *patient registry* is an organized system of collected clinical data used to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure. Patient registries can be used to learn about the natural history of disease, to determine clinical effectiveness or medical product or procedure, to measure or monitor safety and harm, and/or to measure quality of care.

Case-Control Studies

Case-control studies are retrospective studies that compare patients who have a disease or outcome of interest (cases) with patients who do not have said disease or outcome (controls). These studies review medical histories to compare how frequently the exposure to a risk factor is present in each group in order to determine, retrospectively, the relationship between risk factors and disease. An example of a case-control study design is the *chart review*.

Chart Reviews

A *chart review* is a retrospective research study that does not involve contact with human subjects. Patients' medical records are reviewed, and data is obtained regarding a particular condition and or treatment. These studies are often aimed at evaluating patient outcomes based on existing disease, diagnoses and medication use. Data obtained from chart reviews is often used to inform and/or improve the design and/or indication of a treatment.

Clinical Trials

Investigational Drug Studies

A drug is defined as a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, a substance (other than food) intended to affect the structure or any function of the body. *Investigational drug trials* are designed to test the safety and efficacy of a medical treatment in humans. They are typically conducted in a series of steps, called *phases*. Each phase is designed to answer a separate research question relevant for to the drug approval process.

- ***Phase I:*** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- ***Phase II:*** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
- ***Phase III:*** The drug or treatment is given to larger groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

- **Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use. These trials are less common than Phase I, Phase II, and Phase III trials, and sometimes are required by the FDA.

Investigational Device Studies

A medical device is defined by the FDA as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis (IVD) of disease and other medical conditions such as pregnancy.

An *investigational medical device* is one that is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device. Large medical device companies typically develop successive iterations of existing devices. Innovative devices are typically developed by start-up companies in which a physician and/or engineer inventor conceives of a device solution to an unmet clinical challenge, initiates the patent process, and builds preliminary device prototypes.

Medical device development can be divided into three phases:

- **Pilot Phase/Feasibility Phase:** The purpose of the pilot phase (starting with first clinical use) is to establish safety and to assist in design of the pivotal trial.
- **Pivotal Phase:** The purpose of the pivotal trial is to generate data that define patient populations in which use of the device is safe and effective
- **Post-market:** The purpose of the post-market trial is to better understand the long-term effectiveness and safety of the device, including rare adverse events.

Combination Products

Some products regulated by the FDA do not fit exclusively into the category of drug or device but are a combination of 2 or more single-entity products (e.g., drug, biological, or device). Examples are drug-eluting stents or drug patches or individual products that are co-packaged together (procedure sets). The FDA formed the Office of Combination Products (OCP) in 2002. The OCP is responsible for classifying each combination product as a drug, device, or biological based on the *primary mode of action* (PMOA).

Specimen Collection

Both observational studies and clinical trials may sometimes involve the collection of human specimens, cells, cell lines, or data obtained from live individuals for research purposes.

Human specimens and samples can be collected as a necessary part of the current research protocol, or they can be stored for future research activities or projects.

Investigators conducting specimen collection research should refer to the Einstein-IRB policy for the [Collection and/or Study of Human Specimens](#).

Future Use of Specimens

Investigators who plan to store specimens collected during the course and as part of an IRB approved research project for future use(s) should ensure the storage and possible future use(s) are described in the research protocol and consent forms. Investigators should adhere to Einstein OHRA policy on the [Collection and/or Study of Human Specimens](#).

The following section should to be included in the IRB approved consent form, if applicable:

- *“Will any of the samples (blood, tissue, DNA) taken from me be used for future research studies?”*

Refer to the [IRB Consent Form Templates](#), and choose the language in Appendix B or C.

Genetic Testing

Studies that require specimen collection for future genetic testing must ensure the corresponding consent forms include appropriate language in the following sections of the Consent Form Template:

- *“Will this study involve genetic research and/or testing?”*
- *“Consent requirements for genetic testing”*

Investigators should follow the consent form template and guidelines of the [corresponding local IRB of use](#).

NIH Genome Wide Association Studies

If the planned or possible future use(s) involve(s) entering material into the NIH Genome Wide Association Studies, this should be described in both the protocol and consent. Investigators should refer to the [HHS NIH Genomic Data Sharing webpage](#) for more information.

Storage of Banked Samples

The [ICTR Biorepository Core](#) provides secure archival sample storage as well as clinically-annotated specimen biobanks for defined research projects. The core serves the human research blood and tissue banking needs of clinical and translational researchers. Samples can be banked by an individual Principal Investigator or by a consortium of investigators. All samples are tracked and archived using a secure tracking database. The facility works under the best practices set out by NCI and ISBER (2006) for collection, storage, and retrieval of human biological materials for research. To access the core’s services, please utilize the [Analytical Core Lab & Biorepository Service Request Form](#).

Sharing Samples between Institutions

Some clinical research involves sharing specimens and/or biological samples between investigators at different institutions. Investigators with protocols requiring the transfer of specimens or other biological across institutions require a Material Transfer Agreement (MTA).

Material Transfer Agreement (MTA)

A *Material Transfer Agreement (MTA)* is a contract governing the exchange of patented and non-patented biological and non-biological material for research and occasionally other purposes within the scientific community, including academic institutions, other nonprofits and industry. An MTA is a legal contract between the owner of the material (Provider) and a party requesting permission to obtain and use the material for research purposes (Recipient). MTAs typically cover the transfer of a variety of types of material, including cell lines, DNA clones, antibodies, animal models and other reagents.

When Montefiore and/or Affiliate is the Recipient

A MTA is required when MMC or a MMC affiliate is the recipient of the material. Incoming MTAs involve situations in which MMC investigators request material from an academic, nonprofit or commercial entity. IRB review of the protocol is required in these cases. Investigators at MMC must contact [The Office of Clinical Trials \(OCT\)](#) for management. Investigators at Albert Einstein College of Medicine must contact the [Office of Biotechnology](#) for management.

When Montefiore and/or Affiliate is the Provider

An MTA is required when MMC or a MMC affiliate is providing the material to an external entity. Outgoing MTAs involve situations in which MMC provides material to nonprofit or commercial entities that request it. Investigators at MMC must contact [The Office of Clinical Trials \(OCT\)](#) for management. Investigators at Albert Einstein College of Medicine must contact the [Office of Biotechnology](#) for management.

IRB review of the protocol is not required if the samples are coded or de-identified. For IRB review and guidance of your Agreement needs, complete the [Research Agreement Request Form](#) via the Office of Human Research Affairs webpage.

Hazardous Goods Shipping

All investigators, clinicians and research personnel that are shipping biohazardous materials (i.e. blood and tissue specimens, radioactive materials, chemicals, etc.) must complete IATA (International Air Transport Association) certification. Shipping these materials without certification can result in an institutional fine of up to \$60,000 for each offense. You can find more information about IATA certification at [CITI Shipping and Transport of Biological Materials](#). If you have any questions about whether you need IATA certification, please contact Ms. ManYu Chen at mchen@montefiore.org or Mr. Jack Zencheck, Chief Procurement Officer, at 718-430-8889 or izenchec@yu.edu.

CLINICAL RESEARCH ADMINISTRATION OFFICES AND RESOURCES

Clinical research activity is managed and directed by a collection of institutional administrative offices across Montefiore Medical Center (MCC) and Albert Einstein College of Medicine (AECOM). Each office plays a particular role in the administration and supervision of clinical research. Despite differences in scope, these offices share the common goal of executing and promoting safe, effective, and meaningful clinical research at MMC and its affiliates.

The Institute for Clinical and Translational Research (ICTR)

The [Institute for Clinical and Translational Research \(ICTR\) at Montefiore and Einstein](#) is sponsored by the CTSA Consortium -a group of medical research institutions working together to improve the way biomedical research is conducted across the country, is funded by the National Institute of Health (NIH). The consortium shares a common vision to improve patient treatment by reducing the time it takes to develop laboratory discoveries and to engage communities in clinical research efforts.

Investigators looking to initiate their own clinical research protocols and/or in need of resources to execute a clinical research study can contact the ICTR for support. Types of support include:

- Biomedical research informatics
- Biomarker analytical research
- Microgrants
- Biostatistical support
- Clinical research services at the Clinical Research Center (CRC)
- Clinical trial support and management via the Office of Clinical Trials (OCT)

The services provided by the Institute for Clinical and Translational Research Cores are listed below in further detail. To access services, please enter your request in the [portal](#).

Research Education and Training Core

The ICTR supports a highly integrated core of education and career development programs in clinical and translational research. Among our interlinked and coordinated education and career development programs are the innovative PhD in Clinical Investigation (PCI) that identifies, educates, supports, and mentors talented PhD and MD-PhD candidates to become impactful and successful scientists, the Master of Science in Clinical Research Methods (MSc) through the Clinical Research Training Program (CRTP) and two other Core offerings: 1) Clinical Research 101 lecture series entitled Fundamentals of Clinical Research Methods and 2) a seminar program entitled Design and Conduct of Clinical Research.

Research Career Development Core

Einstein's comprehensive selection of career development and educational programs helps faculty pursue careers as clinical and translational scientists in academic and other settings. The Core focuses on new innovative initiatives, including methodologically-focused 'tracks' within our Clinical Research Training Program and novel applications of distance- and hybrid-learning technologies, team science competencies, linking research and health improvement within a learning healthcare system, and providing sustainable career pathways for diverse clinician-investigators in research/healthcare teams.

- i. Mentored for Translational and Team Science (MeTTS)
- ii. CTSA KL2 Grant Awards (Excellence in Promoting LHS Operations & research at Einstein/Montefiore, EXPLORE)

Biostatistics, Epidemiology and Research Design Core (BERD)

The Core is comprised of faculty with expertise in clinical trials, population-based research, and genetic analytic methods, and who provide a wide range of consultation and assistance, including study design, biostatistics analyses, and novel methodologies. The resource provides statistical and epidemiologic support, collaborates with investigators, and identifies new problems and statistical method solutions. Walk-In Biostatistics Consulting is available on both campuses, where investigators can drop by and receive advice about their projects from statisticians.

The [BERD House](#) online portal has resources on preparing a data set, statistical methods, statistics software, and statistics training opportunities.

Research Informatics Core (RIC)

The Core supports the clinical data pipeline for Einstein and Montefiore, and provides informatics infrastructure, tools, and standards that optimize collection, retrieval, integration, sharing, processing, and communication of biological, clinical, and environmental data for clinical and translational research. The Core is a trans-disciplinary service that brings expertise from the Center for Health Data Innovations to support translational research across the spectrum.

Health Research Implementation Core

The health research implementation core provides resources for designing and implementing research programs that efficiently translate effective strategies to improve health into practice in clinical settings and the community through expertise in patient centered outcomes research (PCOR), comparative effectiveness research (CER) and dissemination and implementation science (DIS). The core partners from the Montefiore CMO, the Office of Community and Population Health, and the Montefiore Medical Group.

Clinical Investigation Services Core (CISC)/Clinical Research Center (CRC)

The Clinical Research Center (CRC) units are dedicated to patient-oriented research on both East (Einstein) and West (Moses) Campuses. The units provide staff and dedicated space for adult and pediatric studies. Facilities are available for physical exams, intensive procedures, private interviews, and most types of data collection. Inpatient beds are also available on a *per diem* basis.

Lifespan Research Core

The Core integrates Special Populations and Life Span Research to support clinical and translational research in unique groups across the life span by using novel approaches to enhance the integration of life course research perspectives. The Core engages individuals from disadvantaged ethnic/racial minority groups, or those who bear a disproportionate burden of disease, and focuses on building capacity in rare disease research, Latino health, chronic kidney disease, and HIV by leveraging CTSA cores, training, education and novel methodologies.

Biorepository Core (BioR)

Patient-derived specimens are essential to research in genomics, proteomics, and biomarkers. This core provides banking for biological fluid and tissue specimens as well as human DNA and RNA. The Biorepository provides secure archival sample storage as well as clinically-annotated specimen biobanks for defined research projects. Samples can be banked by an individual PI or by a consortium of investigators. The facility works under the best practices set out by NCI and ISBER for collection, storage, and retrieval of human biological materials for research.

Biomarker Analytic Research Core (BARC)

The Biomarker Analytic Research Core (BARC) is a centralized ICTR translational technologies resource. Patient samples that are handled on both campuses are routed through the BARC. The analytic functions include stable isotope dilution assays, radioimmunoassays, biomarker and substrate analyses, and sample/DNA processing. In addition, we provide high-throughput analyses using mass spectrometry and other methods for a wide range of analyses.

Community Engagement Consultation & Collaboration Core (CECC)

The Core is closely allied with the new Health Research Implementation Core to enhance community engagement with research that impacts health care. The Core works with The Bronx Health Link to expand collaborations and engagement with the Bronx community and healthcare partners. It helps advance life span, child health, and aging research across genders and special populations, by working with the Bronx Community Research Review Board. Finally, the Core innovates methods and processes that advance clinical research by linking with the Community Engagement Research Academy (CERA) to advance team science.

Project Acceleration Resource (PAR)

Translational research can be a complex enterprise, since any single project involves multiple team members, scientific expertise, and resources. The Project Acceleration Resource (PAR) helps coordinate ICTR resources and can help investigators streamline and enhance project implementation by integrating expertise, and facilitating efficient access to resources. The PAR will also provide budget development and grant application support for junior investigators, as well as comprehensive planning support for development of multi-function program grants. Investigators should visit the [PAR website](#) for more information.

Bronx CREED Document Translation Service

The Institute for Clinical and Translational Research in partnership with The [Bronx Center to Reduce and Eliminate Ethnic and Racial Health Disparities \(Bronx CREED\)](#) provide English-to-Spanish document translation by a certified translator for research-related documents, including consent forms, educational materials, and questionnaires. For investigators without external funding there will be no charges. For investigators with external funding budgeted for translation, charges, if any, will be determined on a case-by-case basis. To request translation services, contact Bronx CREED's Scientific Director and Research Core Director, Joel Zonszein, M.D. at (718) 904-2883 or joel.zonszein@einsteinmed.edu.

The Office of Clinical Trials (OCT)

The Office of Clinical Trials (OCT) is the central administrative office for private funded research for Montefiore Medical Center and Albert Einstein College of Medicine. OCT assist the research community with pre and post award management. Services include education and ongoing training, contract and budget development, negotiation and approval, project financial management, business development and administration of an array of research technology tools.

Please visit the [Office of Clinical Trials](#) to review their policies and procedures.

The Biomedical Research Alliance of New York (BRANY)

The Biomedical Research Alliance of New York (BRANY) is a national organization providing support services to sponsors and investigators involved in research in a wide variety of therapeutic areas, medical devices, biologic and diagnostic trials. BRANY's services include:

- Site identification, initiation, and support
- Central IRB
- Quality assurance oversight
- Financial management
- Personnel training to advance the field of clinical research.

All [Industry – Sponsored](#) clinical trials taking place at MMC and its affiliates should utilize BRANY for contractual and budgetary management. Investigators of industry-sponsored

clinical trials should visit the [Biomedical Research Alliance of New York \(BRANY\) website](#) for guidance.

Institutional Review Boards (IRB)

An Institutional Review Board (IRB) is a committee, operating under federal regulations, state laws, and institutional policy, that reviews research involving human subjects to ensure the ethical and equitable treatment of those subjects. All research involving human subjects requires IRB review. An IRB is authorized to review and to approve, defer and/or require modifications to secure approval, table, or disapprove human subject research. Composed of scientists, doctors, lawyers, and lay persons, the IRB ensures that appropriate steps are taken to protect the rights and welfare of participants as subjects of research taking place at Montefiore Medical Center and/or its affiliates. Research matters reviewed by IRBs include:

- Subject safety and privacy via Degree of Risk
- Inclusion and Exclusion of participants
- Recruitment Plans
- Adequacy of the Informed Consent Form
- Quality and Integrity of Data (during an Audit)

Written IRB approval must be obtained before any human subject research activity begins. Per federal regulation, research that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by other officials of the institution.

As a rule, any research taking place at Montefiore Medical Center, Einstein and/or its affiliates involving the use of human subjects or human tissues must be reviewed and approved by an IRB. Montefiore and Einstein have access to two separate IRBs, our own internal Einstein IRB (via Office of Human Research Affairs or OHRA), and an external central IRB managed by [The Biomedical Research Alliance of New York \(BRANY\) IRB](#). All investigator-initiated protocols and those derived from federally sponsored studies are to be reviewed internally by the Einstein IRB. While industry sponsored protocols may be reviewed by either IRB, we are currently directing all industry sponsored trials to the BRANY IRB for review. Both local IRBs are described in further detail below:

Einstein Office of Human Research Affairs (OHRA)

The [Einstein IRB](#) has two committees - the West Campus committee and the East Campus committee. The committees are centrally managed and work to facilitate excellence in human research by extending guidance and support to the research community through high quality review of human subject research. Meetings are held twice a month to review full board items, while all other transactions are reviewed upon receipt on an ongoing basis. Investigators should refer to [The Einstein OHRA's Policies and Procedures](#) for obtaining review and approval of clinical research.

The Biomedical Research Alliance of New York (BRANY) IRB

Investigators conducting industry sponsored clinical research must utilize the [BRANY IRB](#)

for review of their protocol and study materials. The BRANY IRB is a division of [The Biomedical Research Alliance of New York \(BRANY\)](#), an organization founded by the following institutions: Montefiore Medical Center, Mount Sinai School of Medicine, NYU School of Medicine, North Shore – Long Island Jewish Health System, and St. Vincent’s Catholic Medical Centers. The BRANY IRB has been contracted by Montefiore Medical Center, to review human subject research taking place at the institution and its affiliates, to ensure that the rights and welfare of those research subjects are protected. Investigators should refer to BRANY’s policies and procedures for obtaining review and approval of clinical research trials.

For information on federal regulations describing the mandate and operations of IRBs please review the [Code of Federal Regulations 45 CFR 46](#).

The Office of Research Sponsored Programs (ORSP)

The Office of Research Sponsored Programs (ORSP) is the administrative body that manages federally funded research grants for Montefiore Medical Center (MMC). Government-funded research including sub-awards granted to Montefiore Medical Center should be submitted to the ORSP for management. For guidance on ORSP Policies and procedures contact their office 718-920-4151.

The Office of Grant Support (OGS)

Investigators at Albert Einstein College of Medicine (AECOM) intending to conduct federally funded research should contact The Office of Grant Support (OGS). OGS provides pre-award administrative assistance to the entire AECOM, Inc. community, and manages federally funded research including sub-awards granted to Albert Einstein College of Medicine. The office aims to enable faculty scholars to submit competitive grant proposals and to successfully manage all subsequent non-financial responsibilities of the award, resubmission, and renewal processes. For more information please visit the [Office of Grant Support webpage](#).

Research Billing Compliance

The Research Billing Compliance Office ensures that Montefiore Medical Center is in compliance with all laws, regulations and contractual obligations pertaining to the billing of research-related charges for patients covered by Medicare, Medicaid and other third-party payers. Laws and regulations include: Medicare, Medicaid and state insurance laws addressing coverage and payment for clinical services. Contractual obligations include: contracts with the sponsor of the clinical research and those with third-party payers.

Research billing is a critical compliance concern for Montefiore Medical Center. All clinical research activity conducted at Montefiore Medical Center and its affiliates must be compliant with the [Research Billing Compliance Policy and Procedure](#) to ensure that research and standard of care procedures are distinguishable and billed for accordingly.

National Clinical Trial Numbers

The Centers for Medicare and Medical Services (CMS) requires that National Clinical Trial Number (NCT Number) be reported on all billing claims for items/services related to a qualifying clinical trial. The NCT number is obtained when the trial is registered in the National Library of Medicine (NLM) via the [ClinicalTrials.gov](https://clinicaltrials.gov) website (See [Registration Requirements for Clinical Trial Protocols](#)). The NCT Number is an 8-digit number preceded by the letters "NCT." The CMS uses the NCT number to identify and track all items and services provided to beneficiaries during participation in a clinical trial.

Office of Biotechnology and Business Development

The Office of Biotechnology serves as the technology transfer office of Albert Einstein College of Medicine, facilitating the licensing of college technology to industry and research collaborations between industry and faculty. The Office of Business Development serves to further enhance the value of the college's research, clinical and intellectual property assets by proactively collaborating with the commercial, governmental, financial and entrepreneurial communities in novel initiatives. Together, the offices work in partnership and build upon each other's strengths, in order to fulfill the mission of assisting the translation of basic research advances made at Einstein into clinical applications that can benefit the public.

The Albert Einstein College of Medicine retains assignment of all patents granted to its faculty. The college, through its Patent Committee, provides a mechanism for internal peer review and encouragement for its faculty to pursue patenting of technologies that are novel and have clear-cut, practical applications in biology and medicine. These applications have broad utility in biotechnology, clinical diagnostics and pharmaceutical medicine. The college is interested in promoting industry-sponsored research on campus and the commercial development of products derived from our research activities.

For information about the office's policies on patenting and working with industrial partners, as well as technologies available for licensing, please visit their [website](#).

Administrative Committee Approvals

Investigators are responsible for ensuring that all appropriate personnel are informed of his/her potential clinical research study and obtaining approvals where necessary. Below are examples of individuals and/or institutional bodies that may be required to review a clinical research protocol prior to the commencement of research activities.

Department Chair

All investigators must obtain approval from their departmental chairs prior to conducting any clinical research activity.

Dean of Students – Albert Einstein College of Medicine

If AECOM students are among the *Key Personnel* for any study, prior written permission must be obtained from the Einstein Dean of Students.

Pediatrics

Researchers who plan to involve children as research subjects must obtain the signature of the Chair of Pediatrics on the IRB application signature page, unless investigators are submitting to the BRANY IRB, which does not require this signature. All studies involving pediatric patients must be submitted to the Pediatric Protocol Review Committee (PPRC) for review and approval, prior to submission to either the Einstein or BRANY IRB for review and approval.

Investigational Drug Service (IDS)

Some studies require the use of the Investigational Drug Service (IDS) at Montefiore Medical Center, also referred to as the Research Pharmacy, to store, dispense, and manage investigational drugs in a clinical trial. Researchers who plan to store investigational drugs outside of the pharmacy must obtain written approval from the IDS. Investigators not utilizing the Research Pharmacy must obtain a Pharmacy Waiver. Personnel should contact mmcids@montefiore.org for guidance.

Nursing

If the research plan requires the direct assistance of members of the Department of Nursing, the Director of Nursing must sign the IRB application signature page.

Cancer Center Protocol Review and Monitoring Committee (CCPRMC)

Investigators who intend to conduct any research involving a primarily cancer patient population must submit their study protocol to the Cancer Center Protocol Review and Monitoring Committee for review and approval prior to submitting to the IRB. This is the case regardless of the study's funding source (e.g. Federal or Industry sponsored) or which IRB will review the study (e.g. Einstein or BRANY IRB).

However, studies receiving "expedited" review by the CCPRMC may be reviewed by the IRB prior to CCPRMC approval, but IRB approval will not be issued until after the PRMC issues official approval.

Investigators should contact Rutvi Patel at rupatel@montefiore.org or 718-379-6866 for guidance.

Magnetic Resonance Research Center (MRRC)

Investigators who intend to utilize the Gruss Magnetic Resonance Research Center facility must submit their research protocols to the MRRC for review and approval prior to initiating clinical research activity in the MRRC. Please note that MRRC review may lead to modifications of the research protocol. IRB review and approval may be given prior to MRRC submission.

Investigators may visit the [MRRC webpage](#) for more information or contact Parina Shah at parishah@montefiore.org or 718-920-6267.

NBHN Research Protocol Working Group (RPWG) and Health and Hospitals Corporation (HHC)

Investigators who intend to conduct any research involving the Health and Hospitals Corporation (HHC), New York Medical Association, North Bronx Health Network, Jacobi Medical Center, or North Central Bronx personnel, facilities, and/or resources must submit their research protocols to the North Bronx Health Network Research Protocol Working Group (RPWG) and Health and Hospitals Corporation (HHC) for review and approval prior to conducting research at any of the aforementioned sites. The IRB may review protocols in tandem to RPWG) and HHC submission.

Investigators should contact Howard Nadel at howard.nadel@nbhn.net or 718-918-7070 for guidance.

Institutional Safety Committees

Some clinical research protocols require review and approval by institutional safety committees prior to obtaining Institutional Review Board (IRB) review and approval. This is the case regardless of whether a clinical research study is submitted to the Einstein IRB or BRANY IRB. Investigators are responsible for ensuring that all appropriate personnel are informed of his/her potential clinical research study and obtain approvals where necessary. Below is a list of institutional safety committees, and the types of studies that require their review.

Einstein Institutional Biosafety Committee (IBC)

Investigators who intend to conduct any research involving the transfer of gene material, complementary DNA, full length genes, RNA, or oligonucleotides into humans must submit their research protocol to the Institutional Biosafety Committee (IBC) for review and approval, prior to submitting to the IRB. This is the case regardless of the study's funding source (e.g.: Federal or Industry-sponsored) or which IRB will review the study (e.g.: Einstein or BRANY IRB).

Investigators should contact Delia Vieira-Cruz at delia.vieira-cruz@einstein.yu.edu or 718-430-3560 for guidance.

Radiation Safety Committee (RSC)

Investigators who intend to conduct any research involving radiation or radioisotopes beyond standard clinical care at Montefiore Medical Center or its affiliates must submit their research protocols to the Radiation Safety Committee (RSC) for review and approval prior to conducting any clinical research activity. Investigators may submit their protocols to the RSC and the IRB simultaneously. However, RSC approval is required before the IRB approves the study.

Investigators should contact Manyu Chen at mchen@montefiore.org or 718-920-5012 for information on submitting protocols for RSC review.

Required Committee Approvals Table

COMMITTEE NAME	REQUIRED FOR	WHEN?	CONTACT
Einstein Institutional Biosafety Committee (IBC)	Any research involving the transfer of gene material, complementary DNA, full length genes, RNA, or oligonucleotides into humans	Before submitting to the IRB for review	Delia Vieira-Cruz (718-430-3560)
Cancer Center Protocol Review and Monitoring Committee (CCPRMC)	Any research involving a primarily cancer patient population. (Note: Studies receiving "expedited" review by the PRMC may be reviewed by the IRB prior to PRMC approval, but IRB approval will not be issued until after the PRMC approves.)	Before submitting to the IRB for review	Rutvi Patel (718-379--6866)
Pediatric Protocol Review Committee (PPRC)	Any research involving a pediatric patient population	Before submitting to the IRB for review	Alan Fleischman, MD (718-741-2333)
Clinical Research Center Protocol Review Committee (CRC PRC)	Any research utilizing the CRC facilities	Before receiving IRB Approval; may submit to both offices in tandem	Elizabeth Castro (718-920-5126) or Minka Chikaloreva (718-920-5174)
Radiation Safety Committee (RSC)	Any research involving Radiation or Radioisotopes beyond standard clinical care at Einstein/Montefiore.	Before receiving IRB Approval; may submit to both offices in tandem	Manyu Chen (718-920-5012)
Magnetic Resonance Research Center (MRRC)	Any research involving the MRRC facility, <u>prior</u> to initiation the MRRC component of the study. Please note that MRRC review may lead to modifications of the research protocol.	Before beginning research activity in MRRC	Parina Shah (718-920-6267)
NBHN Research Protocol Working Group (RPWG) and HHC	Any research involving HHC/NYMA/NBHN/JMC/NCB personnel, facilities, and/or resources.	Before beginning research activity at these sites	Howard Nadel (718-918-7070)

SPONSORSHIP

In clinical research, the individual or entity that originates and directs the clinical research plan or protocol is referred to as the *sponsor*. Many different types of sponsorship arrangements are possible. Typical sponsor responsibilities may include all or some of the following:

- Funding or material support, such as investigational drug or device
- Authorship of the research plan
- Ongoing monitoring of the investigation
- Data assembly and analysis

Note: If an entity provides sponsorship that is only financial, the entity would be considered a financial sponsor but not a sponsor in terms of the execution of the research plan.

If industry funding is provided, the sponsor- investigator should contact [The Office of Clinical Trials](#) for guidance. If any federal funding (incl. NIH and co-sponsorship) is provided for the study, the investigator should contact [The Office of Research Sponsored Programs](#) if the award will be granted to Montefiore Medical Center or [The Office of Grant Support](#) if the award will be granted to AECOM.

Examples of research sponsorship include:

Industry Sponsorship

Industry-sponsored studies are usually clinical trials that are financially funded and managed by a pharmaceutical or biotechnology company that is investigating a drug, device, treatment, or new use thereof. However, sometimes clinical research studies that are not trials may also receive industry sponsorship. Multiple institutions may collaborate on these industry-sponsored trials or studies. Data are sent to the sponsoring company or designated [Contract Research Organization \(CRO\)](#) for analysis. Investigators of industry-sponsored research should contact the [Office of Clinical Trials](#) for guidance.

The Sponsor-Investigator (Investigator-Initiated Research)

The term *Sponsor-Investigator* is applied to an individual who both initiates and conducts an investigation, and under whose immediate direction an investigational product or treatment is administered or dispensed (for drug and device trials), and the protocol is executed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.

A sponsor-investigator would typically:

- Author the research plan
- Personally, hold any FDA IND/IDE for clinical trials
- In a multi-center study
 - Select qualified investigators
 - Provide investigators with the information they need to conduct the investigation properly (incl. Investigator Brochure)
- Ensure proper monitoring of the investigation
- Ensure that the FDA, any reviewing IRBs, and all participating investigators are promptly informed of significant new information about an investigation, including significant new adverse events or other risks of the test article.
- Ensure that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations

- Protect the rights, safety, and welfare of subjects under the investigator's care
- Control drugs, biological products, and devices used in the investigation

Clinical research conducted by sponsor-Investigators is typically referred to as an *investigator-initiated study*. Investigator-initiated studies may be funded by private industry, consortiums/foundations, local, state, or federal government, or by the investigator's academic or clinical department.

Federal Sponsorship

The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services (HHS), is the nation's medical research agency. The NIH is made up of 27 [Institutes and Centers](#), each with a specific research agenda, often focusing on particular diseases or body systems. NIH sponsored research may be single or multicenter.

Consortiums and Co-Sponsorship

Some trials may be co-sponsored by several groups or individuals.

RESEARCH PERSONNEL

Clinical research usually involves several teams of people with a variety of roles and specialties. The following is a description of the different types of research personnel that may play a part in the clinical research conducted at Montefiore Medical Center and its affiliates.

The Local Research Team

An individual that participates in a substantive aspect of the execution research plan is considered *Key Personnel*. Key Personnel must be listed on the original IRB application, or added by amendment prior to participating in any substantive aspect of the research. Additionally, the following departments must be made aware of all Key Personnel and any changes to Key Personnel immediately:

- [Department Chair](#) or [Dean of Students](#) – only PI or Sub-I information
- Corresponding contracts and budget management office:
 - [Office of Clinical Trials \(OCT\)](#)
 - [Biomedical Research Alliance of New York \(BRANY\)](#) (including its IRB)
 - [Office of Research Sponsored Programs \(ORSP\)](#)
 - [Office of Grant Support](#)
- [Einstein Institutional Review Board \(Einstein IRB\)](#) –if utilized
- [Investigational Drug Service \(Research Pharmacy\)](#) – for investigational drug studies
- [Clinical Research Center \(CRC\)](#) – if services are utilized
- [Biorepository Core](#) - if services are utilized

Principal Investigator (PI)

The *Principal Investigator (PI)*, also called the Clinical Investigator, is responsible for personally conducting and supervising the conduct of clinical research and for protecting the rights, safety, and welfare of the subjects enrolled in the research. Investigators commit themselves to personally conduct or supervise the study. When tasks are delegated by a PI, the PI is ultimately responsible for providing adequate supervision of those to whom tasks are delegated. The PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

The PI should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and New York State licensure where relevant) to perform the delegated task. In all cases, a qualified physician (or dentist) should be responsible for all research-related medical (or dental) decisions and care, and the delegated tasks should be within the delineation of privileges for the individual.

The PI should maintain a list of the appropriately qualified persons to whom significant research-related duties have been delegated (typically called a Delegation of Authority Log). This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., can refer to an individual's CV on file), and identify the dates of involvement in the study. The PI should maintain separate lists for each study conducted by the PI.

The PI should have sufficient time to properly conduct and supervise the clinical research study. The level of supervision should be appropriate to the staff, the nature of the study, and the subject population. The PI should develop a plan for the supervision and oversight of the clinical research study at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced.

Principal investigators are required to conduct the study in accordance with the IRB approved protocol but their responsibility extends beyond the scientific conduct of the study and includes: compliance with federal/state laws, institutional policy, and the terms/conditions of the sponsor's grant, as well as fiscal management, and supervision of the research team.

Investigator Eligibility

All full-time, part-time, emeritus, AECOM associates with faculty appointments at Montefiore Medical Center and its affiliates are eligible to serve as Principal Investigators and Project Directors. Other professional staff holding titles typically associated with independent work may also serve as Principal Investigators. All Project Directors or Principal Investigators must have the approval of their Departmental Chairs indicated by the Chair's signature on the internal grant application form.

Investigators must meet criteria outlined in the [OHRA Policy describing Investigator Qualifications](#) in order to be a Principal Investigator. Nurses or other clinical

professionals with a PhD degree or individuals who conduct research in the course of their employment at Montefiore, but do not have a faculty appointment may, in some cases, act as PI for research that is not greater than minimal risk. Contact the [Einstein OHRA](#) for more information.

The following is a description of the responsibilities of all Principal Investigators at Montefiore Medical Center and its affiliates, in further detail:

PI Responsibilities

- Obtaining IRB approval before beginning any non-exempt human subjects research; PIs are responsible for providing the IRB with sufficient information and related materials about the research (e.g., grant applications, research protocols, sample consent documents) so that the IRB can fulfill its regulatory obligations, including making the required determinations under 45 CFR 46.111 and, if applicable, subparts B, C and D;
 - Obtaining and documenting informed consent of subjects or subjects' legally authorized representatives prior to the subject's participation in the research, unless these requirements have been waived by the IRB;
 - Ensuring that a copy of the informed consent document is given to each research subject (or the subject's legally authorized representative), and keep the signed original for their records;
- Obtaining prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and document, except those necessary to eliminate apparent immediate hazards to subjects;
- Ensuring that progress reports and requests for continuing review and approval are submitted to the IRB in accordance with the policies, procedures, and actions of the IRB as referenced in the institution's OHRP-approved Federal Wide Assurance;
- Timely fulfillment of requirements associated with continuing review prior to the expiration date of the current IRB approval; continuing review and approval of research studies is required so long as the research study is ongoing (research-related interactions and interventions with human subjects) or the obtaining and analysis of identifiable private information described in the IRB-approved research plan have been completed;
- Prompt IRB reporting of any unanticipated problems involving risks to subjects or others, in accordance with Institutional IRB policy;

- Prompt reporting of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB, in accordance with Institutional IRB policy;
- Pertinent record keeping as required by HHS regulations for at least three years after completion of the study;
- Study completion notification to the IRB, corresponding contract management office (OCT, BRANY, Grants Support, ORSP), Pharmacy, CRC, and Biorepository, as applicable.
- Continue honoring any confidentiality protections of the data after study completion and closure;
- Honoring any other commitments that were agreed to as part of the approved research, for example, providing information about the study results to research subjects, or honoring commitments for compensation to research subjects for research participation.

Collaborating Investigators (Sub-Investigators)

A sub-investigator is any research team member, other than the principal investigator, who assists with the design and execution of the investigation, works under the direction of the PI, but does not actually direct its conduct but rather assists and covers for the PI in his/her absence. Important study-related procedures and decisions may be delegated to a qualified sub-investigator. Sub-investigators are designated and supervised by the PI and should be qualified by education and professional experience to perform the tasks delegated to them. All sub-investigators must be listed as key personnel on the IRB application or added by amendment.

Study Coordinator

A Study Coordinator, sometimes called Clinical Research Coordinator, is an integral part of the study team who typically prepares reports and applications, reviews research participant records, abstracts data, completes case report forms (CRFs) and arranges study appointments. The study coordinator generally works closely with the participants, Principal Investigator and study monitor.

Investigational Pharmacist

An investigational pharmacist assists with the design and/or execution of the randomization scheme, compounding, storage, dispensing and blinding of the Investigational Product for a clinical trial.

Biostatistician

A collaborating biostatistician assists with formalizing the research hypothesis, identifying the specific aims to be addressed, selecting primary and secondary outcome measures, randomization and stratification strategies, statistical modeling, balancing sample or selection size vs. power, monitoring data safety and security and the selection and

implementation of a statistical analysis strategy. [Industry-Sponsors](#) of clinical research trials usually provide their own biostatistician. [Sponsor-Investigators](#) conducting their own clinical research ([Investigator-Initiated](#) research) may require biostatistical support; institutional biostatistical support can be obtained via the [Biostatistics, Epidemiology, and Research Design Core \(BERD\)](#).

Residents and Fellows

Residents and fellows may participate in research that is directed by a Montefiore/Einstein faculty member. As Principal Investigator, the faculty member directs the investigation and delegates study-related tasks based on the resident's / fellow's prior experience, qualifications, and institutional policy. Residents and fellows generally are not Principal Investigators. Residents and fellows who engage in research must be included as Key Personnel on the IRB application or added by amendment prior to participating in the research.

Medical Students

Medical students may participate in research that is directed by a Montefiore/Einstein faculty member. As Principal Investigator, the faculty member directs the investigation and delegates study related tasks based on the student's prior experience, qualifications, and institutional policy. Medical students who engage in research must be included as Key Personnel on the IRB application or added by amendment prior to participating in the research. Participation of medical students requires the written approval of the Einstein Dean of Students.

The Sponsor's Team

The management of a clinical research study, including commercial drug or device trials, may be overseen by an external Sponsor (industry sponsor, usually, for drug/device trials) or a [Contract Research Organization \(CRO\)](#). A CRO is a company contracted by the sponsor to oversee the research on the sponsor's behalf.

Sponsor-investigators of investigator-initiated studies should expect to coordinate, supply, and manage the following roles and responsibilities at the local and/or external sites for multi-site studies.

The sponsor's responsibilities generally include:

- Funding or material support
- Authorship of the research plan
- Data assembly and analysis
- Selecting qualified investigators
- Providing investigators with the information they need to conduct the investigation properly
- Ensuring proper monitoring of the investigation
- Ensuring that the FDA, any reviewing IRBs, and all participating investigators are

- o promptly informed of significant new information about an investigation, including significant new adverse events or other risks of the test article, for clinical trials.
- o Ensuring that reports to the FDA and any reviewing IRBs are submitted as required, for clinical trials

The following individuals typically manage the study on behalf of a sponsor/CRO:

Medical Monitor (MM)

The Medical Monitor is typically a physician, retained by the sponsor and who evaluates adverse events, unanticipated problems and other data as the study progresses and provides consultation to the local study team as needed.

Project Manager (PM)

The Project Manager is the “team lead” and may assist with site start-up activities, coordination of the shipment of specimens, study instruments, investigational product/device, and management of [Clinical Research Associates \(CRA\) or Site Monitor](#), if applicable. Any issues that cannot be resolved by the local site’s CRA are generally directed to the PM.

Clinical Research Associate (CRA) or Site Monitor

The CRA/Site Monitor, often referred to simply as “monitor,” is the principal point of contact for the site study team. The CRA typically visits the site at regular intervals for monitoring of the study data. See [Monitoring](#) section of this document for more information.

Data Coordinating Center (DCC)

The Data Coordinating Center (DCC) processes all data collected on the [Case Report Forms \(CRFs\)](#). The DCC may generate “queries” or *Data Clarification Forms (DCFs)* when there are inconsistencies, unexpected or out of range entries on the CRFs. See the [Queries](#) section of this document for more information.

Contract Research Organization (CRO)

Often times, industry sponsors partner with a Contract Research Organization (CRO), also referred to as a *Clinical Research Organization*, in order to speed up the drug development and approval process. A CRO is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries on a contractual basis. A CRO may assist with services like biopharmaceutical development, biologic assay development, commercialization, preclinical research, clinical research, clinical trials management, and pharmacovigilance. CROs can vary in size from large, international full-service organizations to small, niche specialty groups.

Many CROs focus on providing clinical trial support services for drugs and/or medical devices. CROs that specialize in clinical trials services can offer pharmaceutical companies the expertise of moving a new drug or device from its conception to FDA/EMA marketing

approval. Pharmaceutical companies also benefit from not having to maintain a staff for these services.

PRE-STUDY

Before clinical research studies can be executed, they undergo several *pre-study* stages to ensure that research is scientifically sound, and to protect the interests of study personnel, patients, and the institution. Outlined below are some of steps investigators can expect to complete prior to actively conducting clinical research. Applicability may depend on the type of clinical study.

Research Training & Education

There are several opportunities for clinical research training at Montefiore Medical Center. Personnel who are involved in clinical research or intend to conduct clinical research involving MMC patients are welcome to take advantage of these resources. Some resources are mandatory for clinical research personnel and others are recommended based on personnel role.

Good Clinical Practice (GCP) Certification Requirement

The training of clinical research investigators and study teams is crucial to successful translation of novel drugs, devices, treatments, and interventions. In order to secure comprehensive competency-based training for clinical research personnel, all investigators and personnel directly involved in new and ongoing clinical research studies that involve the testing of drugs or devices, including all FDA-registered studies and investigator-initiated protocols, are required to complete *Good Clinical Practice (GCP)* training. This requirement applies to studies reviewed by both the Einstein IRB, and approved external IRBs (e.g. BRANY, NCI CIRB, etc.).

All Montefiore, Einstein and PAGNY employees who participate in clinical research (including faculty investigators) must have certification of completion of GCP training in order to submit a protocol for IRB review and approval.

Any of the programs below will qualify:

- [Collaborative Institutional Training Initiative \(CITI\)](#)
- [Academy of Physicians In Clinical Research \(APCR\)](#)
- [FDA Investigator Course](#)
- [TransCelerate Biopharma, Inc.](#) approved courses
- [National Institute of Allergy and Infectious Disease \(NIAID\) Program](#)
- GCP courses offered by [ACRP](#) or [SOCRA](#).

Please refer to the [Einstein OHRA Good Clinical Practice Education Website](#) for more information and guidance on this policy.

Collaborative Institutional Training Initiative (CITI)

In addition to GCP certification, the Collaborative Institutional Training Initiative (CITI) provides a computer-based training research curriculum. Research personnel at Montefiore Medical Center and its affiliates are recommended to take the [Human Subjects Research](#) series.

To register for CITI courses, visit: <http://www.citiprogram.org>. Once completed, personnel will receive an email from the Office of Academic Affairs containing a memo stating that the CITI course had been completed. Personnel should keep the certificate for their files. When registering for this course, indicate area(s) of research on both the initial registration page and on the final comments page.

Office of Clinical Trials Research Policy and Training Initiative

The [Office of Clinical Trials](#) has developed educational initiatives for investigators and study coordinators with expertise levels ranging from novice to expert. Research personnel interested in more information or participating in these programs may contact the OCT at OCT@montefiore.org.

Lunch and Learn Series

Lunch and Learn is a series of seminars and workshops geared towards the interests and needs of clinical research trial coordinators, research assistants, and research nurses at Montefiore Medical Center. They are held on a monthly basis, on Moses and Einstein campuses. *Lunch and Learn* provides coordinators an opportunity to network with colleagues, and discuss pertinent, timely research topics presented by guest speakers.

Biomedical Research Alliance of New York (BRANY) Institute for Research Education

Montefiore Medical Center has partnered with the Biomedical Research Alliance of New York (BRANY) to offer an online educational opportunity for research personnel. BRANY's courses are led by experts in the fields of research compliance and IRB standards. These classes are recommended for any clinical research professional including principal investigators, research coordinators, research pharmacists, regulatory coordinators, and data managers who need to be familiar with the federal regulations, ethical guidelines, CIP prep, and processes involved in the conduct of human subject research. Programs are offered in the following areas:

It is recommended that all MMC clinical research personnel intending to conduct industry-sponsored clinical trial research complete BRANY's *Fundamentals of Clinical Research* course. This course is a 1-day online program consisting of four modules:

- MODULE 1: Significant Events In Human Research
- MODULE 2: Study Designs
- MODULE 3: Clinical Trial Startup

- MODULE 4: Documentation Of A Clinical Trial

Clinical research personnel may access this course and others via the [BRANY Training Campus](#).

Research Training Education and Career Development Programs (RET)

The [ICTR](#)'s Research Training Education and Career Development Programs (RET) are a series of pre-doctoral and post-graduate opportunities for those interested in advancing their academic research careers. RET's mentored educational and training programs are designed to prepare individuals for a career in clinical research, and to play a role in the transformation of clinical and translational investigation. RET participants will benefit from personal attention from engaged Montefiore-Einstein faculty and peer group collaboration.

Participants on RET's multidisciplinary training and education include:

- Faculty
- Physicians and other health professionals
- Fellows
- Residents
- Ph.D.'s
- Medical students
- Graduate students

Academic and educational opportunities provided by RET include:

- Ph.D. In Clinical Investigation (eCLIPSE)
- Clinical Research Training Program (CRTP)
- Lecture Series: Clinical Research Methods
- Courses in Clinical Trial Conduct
- Research Career Development

RET programs are learner-centered with a focus on the core competencies developed by the NIH's Clinical and Translational Science Award (CTSA) program. They emphasize methods that promote a team-based approach to scientific inquiry. For more information on these programs please visit the ICTR's [Research Training Education and Career Development Program website](#).

Protocol Development

All clinical research begins with a protocol, designed to answer a research question and guide the specifics of research activity. Most [industry-sponsored clinical trials](#) provide investigators with their own protocol, to which investigators must adhere strictly. However, it is possible for investigators to write and design their own protocols, *and* obtain industry sponsorship to help fund the execution of the protocol ([Investigator-Initiated](#) Industry Sponsored Clinical Research).

Writing a Clinical Research Protocol (for Investigator Initiators)

Investigators interested in writing their own protocols must ensure said protocol is scientifically sound and adequately designed as per Einstein OHRA Policies. Investigators are expected to refer and adhere to the [Einstein OHRA's Protocol Elements Checklist](#) for guidance on writing a clinical research protocol. It is also recommended that Investigators refer to the following resources when writing protocols:

- [SPIRIT 2013 Statement](#), peer-reviewed *Annals of Internal Medicine*
- [Drug Protocol Template](#) provided by the ICTR
- [FDA Drug Study Design Information Sheet](#)

Resources for Protocol Design and Development

Investigator-initiators are expected to develop clinical research protocols that are scientifically sound and adequately designed. To help ensure the quality of research protocol design, Montefiore Medical Center (MMC) in partnership with Albert Einstein College of Medicine (AECOM) and the Institute for Clinical and Translational Research (ICTR) make the following resources available to investigator-initiators. It is highly recommended that Investigator-Initiators utilize these resources during their protocol development.

Biostatistics Epidemiology and Research Design (BERD) Core

Investigator-Initiators are encouraged to take advantage of the services provided by the ICTR's Biostatistics, Epidemiology and Research Design Core (BERD). BERD's staff provides assistance and expertise in areas such as data dimension reduction and modeling and overall analysis of results. This support ensures that:

- the study objectives and specific aims of new projects are clearly specified,
- hypotheses are formulated in a way that can be evaluated
- primary and secondary endpoints are appropriately defined,
- sample size and power are sufficient, and
- the analysis is valid and comprehensive.

To book a free consultation for statistical support, investigators should complete the [ICTR Research Informatics Core Service Request Form](#). Additionally, walk-in biostatistics consulting is available at offices on the East and West Campuses. Investigators are invited to drop by and receive advice about their projects from statisticians.

NOTE: Investigator-initiators are also expected to review the [ICH Guidance on Statistical Principles for Clinical Trials](#) when designing their protocols.

Research Informatics Core (RIC)

The ICTR's Research Informatics Core (RIC) assists investigator-initiators by creating computer-based clinical data pipelines for their studies. RIC staff provides

investigators generalized, secured and accountable informatics infrastructure, software tools and standards of practice that optimize the following:

- collection, retrieval, integration and analysis of data,
- sharing of biological, clinical and environmental data among stakeholders,
- data management of specimen storage, identification and linkage with clinical data, and
- provision of a secure storage for clinical, experimental and biosample data

The RIC designs informatics resources based on a “global” model that encompasses multi-institutional, accountable and collaborative research. It then works with investigators to customize these resources to address their individual needs, such as:

- clinical research workflows,
- arrays of data sources,
- methodology and platforms,
- electronic health data,
- personal health records, and
- integrated data repositories

RIC also ensures that these resources adhere to the regulatory and ethical mandates for accountability protection and confidentiality of personal health information. Investigators can request an RIC consultation via the [Core Facilities Services Request Form](#). To facilitate investigator access to informatics services, RIC has office space on the West and East Campuses.

Clinical Looking Glass (CLG)

Clinical Looking Glass (CLG) is an extensive patient database developed by the Department of Outcomes Analysis and Decision Support at Montefiore Medical Center. CLG provides access to a large amount of patient data that can be utilized by investigators and/or Key Personnel to determine whether there are enough patients to justify a formal request of the IRB for to conduct a clinical research project.

Approval forms, CITI course completion, and CLG training are required to gain access. For more information on policies, procedures, and how to access CLG please visit the [Clinical Looking Glass website](#), and review Montefiore Medical Center’s Administrative Policy on the [Appropriate Use of Clinical Looking Glass](#).

Funding Types and Opportunities

Conducting a successful clinical research study can be an expensive undertaking. Clinical research funding can take different forms and come from various sources. Funding types include material support, such as investigational drug or device provision, and/or financial

support in the form of grants or activity based payment. Details regarding the type of funding are outlined in the [Research Agreement](#).

Below is a description of various funding sources, which can provide either material or financial support, or both:

Industry Funding

Most industry funding comes from private (usually pharmaceutical or medical device) companies for the execution of a clinical trial protocol (both Industry-sponsored and investigator-initiated). [Sponsor-Investigators](#) who intend to conduct their research with the support of industry funding should contact [The Office of Clinical Trials](#) for contractual and budgetary management. Principal Investigators of [Industry-Sponsored](#) research protocols should contact the [Biomedical Research Alliance of New York \(BRANY\)](#) for contractual and budgetary management.

Department Funding

Some investigators have established research accounts, which are managed by their clinical department administrator at Montefiore Medical Center. These accounts house funds that have been paid to investigators from previous clinical research activity. Sponsor-investigators may utilize these monies to fund the execution of their (investigator-initiated) clinical research protocols. Sponsor-Investigators looking to fund their own investigator-initiated clinical research should contact [The Office of Clinical Trials](#) for contract and budgetary management.

State/Local/Federal Government Funding

Some clinical research is funded by governmental institutions. Principal Investigators and Sponsor-Investigators who intend to conduct clinical research with any kind form of governmental funding should contact [The Office of Research Sponsored Programs \(ORSP\)](#) if the award will be granted to Montefiore Medical Center or [The Office of Grant Support](#) if the award will be granted to Albert Einstein College of Medicine. These respective offices can also provide guidance on how to obtain such funding.

Funding for Research under a Consortium or Foundation

Clinical research projects may involve several groups or individuals, usually consisting of academic medical professionals or institutions sharing a common vision for medical research or advancement. These groups are referred to as *consortiums*. Medical and academic foundations may also be involved in a particular research project. Consortium or Foundation projects can receive funding from private or government sources. Clinical research receiving funding under a consortium or foundation with private funding is managed by [The Office of Clinical Trials](#). Consortium and Foundation research with government funding being awarded to Montefiore Medical center is managed by [The Office of Research Sponsored Programs \(ORSP\)](#). Consortium and Foundation research with government funding being awarded to AECOM is managed by [The Office of Grant Support](#) at Albert Einstein College of Medicine.

Principal Investigators should contact the appropriate office for contractual and budgetary management.

Foreign Sponsored Research

Any research that is sponsored or funded by a foreign company or group is managed by [The Office of Clinical Trials](#). Contact the OCT for guidance on negotiating and processing these contracts.

Typically, an Investigator is contacted by an external Sponsor and is solicited to participate in a clinical research study. Very little is revealed to the investigator about the study protocol at this stage, until a Confidentiality Disclosure Agreement (CDA) is executed between the sponsor and the investigator's institution. Also known as a "Confidentiality Agreement" or "Non-Disclosure Agreement," a CDA is a legal document that ensures the confidentiality or "secrecy" of information that one party discloses to another party. A fully executed (signed by all parties) CDA enables an investigator to access to the sponsor's final protocol. Executing a CDA is very typical for Industry-Sponsored clinical research trials.

Montefiore Medical Center requires that all CDAs be negotiated and signed by the institution on behalf of the Investigator. Investigators are not permitted to negotiate or sign CDAs individually. Investigators who receive a CDA from an industry-sponsor should contact [The Biomedical Research Alliance of New York \(BRANY\)](#) for guidance.

Sponsor-Investigators, who intend to subcontract external research sites to conduct their clinical research, are encouraged to have the sites sign a CDA, prior to releasing proprietary information. Sponsor-investigators should contact [The Office of Clinical Trials](#) for guidance on establishing a CDA. Investigators who intend to conduct government funded clinical research at should contact [The Office of Research Sponsored Programs \(ORSP\)](#) for management of their CDAs if the award will be granted to Montefiore Medical Center. Investigators who intend to conduct government funded clinical research should contact [The Office of Grant Support](#) at AECOM for management of their CDAs if the award will be granted to Albert Einstein College of Medicine.

Feasibility

Once a CDA has been fully executed, a sponsor will release the protocol to investigator. At this stage, potential investigators are expected to scrutinize the protocol and determine his/her interest, and capacity to conduct the activities expected of him/her as dictated by the protocol. This is called the *Feasibility* stage.

Some key questions for Investigators to consider during the Feasibility stage are listed here:

- *Am I interested in the science being conducted via this protocol?*
- *Do I have access to the appropriate patient population for this study?*
- *Can dedicate the necessary time out of my professional and/or academic schedule to conduct these research activities?*

- *Do I have access to the necessary additional personnel to execute these activities? (study nurse, technologists, research coordinators, etc.)*
- *Which ancillary departments do I need to partner with?*

Feasibility Questionnaire

Once an investigator has determined that he/she would like to participate in the study, he/she may be expected to complete a *Feasibility Questionnaire*. Industry-sponsors may send this questionnaire to investigators in tandem with the final protocol, or the protocol may be sent shortly afterwards. At this point, an investigator will answer several questions pertaining to his or her ability to conduct the study at this site/institution. The sponsor, who may be selecting from various institutions for partnership on the study, utilizes the responses to this questionnaire, among other factors, to help determine which institutions or sites will be participating in this study. Investigators are expected to be realistic in their answers on these questionnaires. It is recommended that investigators use the above referenced questions as a guide to complete the questionnaire.

Clinical Looking Glass (CLG)

Investigators are encouraged to utilize the [Clinical Looking Glass](#) to help determine whether he/she has the adequate patient population as required by the protocol.

Site Selection Visit

A sponsor may conduct a Site Selection Visit (SSV), also referred to as a Pre-Site Selection Visit (PSSV), in order to help determine which sites or institutions will be chosen to participate in the clinical research study. SSVs are a typical step taken by Industry-sponsors, during which time the sponsor views all spaces relevant for carrying out the research protocol activities. This usually includes but is not limited to the clinical settings where patients will be recruited, pertinent laboratories and ancillary departments (Pathology, Clinical Research Center, etc.).

The purpose of the SSV is to review the adequacy of the site, the training and experience of the study staff, the access to the right patient population, and the site's interest in the study. The entire visit usually lasts about 3-4 hours and is followed-up by a report from the sponsor stating whether or not the site has been selected to participate. Before hosting a SSV, Investigators are expected to have the following items completed and/or resolved:

- *Dedicated Study Coordinator who will work out the logistics of the PSSV, in addition to study activities should the PI be selected to participate*
- *Assurance from relevant research personnel within or across departments to participate as necessary in the conduct of the protocol activities*
- *Appropriate ancillary departments (Radiology, Pathology, etc.) should be made aware and agree to the PSSV visit timing/schedule.*
- *Dedicate at least an hour out of his/her day to meet with the Sponsor's representative to discuss any concerns about the protocol.*

If and when an investigator has been selected to participate in the study, as expressed in a post-SSV report from sponsor, Investigators can expect to receive a [Research Agreement](#) from the sponsor, which may include a draft budget.

The Research Agreement

A Research Agreement is a legally binding contract that defines the scope of work required by the protocol, and manages the relationship between the sponsor, that may be providing the financial support, study drug or device, and /or proprietary information, and the institution, that may be providing data and/or results, publication, or input into further intellectual property. A research agreement serves to determine responsibilities, terms of collaboration, requirements for payment and reimbursement, publication and intellectual property terms, indemnification and or insurance, subject injury coverage, guidelines for dispute resolution, grounds for termination of contract, and possibility of amending contract terms in the future.

Sponsors will typically send the draft research agreement directly to the Principal Investigator (PI). If and when the PI receives the draft agreement, he/she should contact the appropriate contract management office as detailed below:

- [Biomedical Research Alliance of New York \(BRANY\)](#) for Industry-Sponsored clinical research.
- [Office of Clinical Trials \(OCT\)](#) for non-government funded consortiums, subcontracts, collaborations between institutions, Investigator-Initiated, and foreign sponsored research.
- [Office of Research Sponsored Programs \(ORSP\)](#) for government-funded research, including sub-awards, taking place at a Montefiore Medical Center campus
- [Office of Grants Support](#) for government-funded research, including sub-awards, taking place at Albert Einstein College of Medicine.

Informed Consent Form (ICF) Development

Informed Consent is the term given to the communication process that allows individuals to make an informed choice about participation in a research study. Freely given informed consent must be obtained from every decisionally capable, potential adult subject before any research procedures begin, unless the IRB has waived some or all of the consent requirements. This consent process is reflected in an Informed Consent Form (ICF) that contains specific, required information about the research study. The ICF serves as the formal authorization by an individual of their agreement to participate in the proposed research.

The Office of Human Research Affairs and BRANY IRBs have developed standard language and format to be used in portions of all research consent documents. This standard language has been developed for those elements of the study that deal with confidentiality, compensation, answers to questions, and the voluntary nature of participation. Sample or draft Informed Consent Forms may be developed by the clinical research sponsor. The IRB of record is the final authority on the content of the consent documents that is presented to the prospective study subjects.

Investigators of Industry-sponsored trials can expect to submit draft consent forms to BRANY's IRB for review. Sponsor–Investigators are expected to develop their own ICFs for their Investigator-initiated protocols in accordance with the [Einstein Office of Human Research Affairs Informed Consent policies and templates](#). Sponsor-Investigators should expect to submit the draft ICFs they have developed to the Einstein IRB for review.

For more information on federal regulations and requirements of the Informed Consent Process, please review the [Department of Health and Human Services \(HHS\) regulations for the Protection of Human Research Subjects \(45 CFR 46\)](#) and [FDA regulations \(21 CFR 50 & 56\)](#).

Study Budgeting

Part of the success of a clinical research project is contingent on the adequacy of its budget. Clinical research studies should include a budget that meets the financial needs of executing the protocol activities. Costs for supplies, equipment, and services can vary nationally. Due to this variety, clinical research budgets are often negotiable.

Research budgets are usually drafted by the study sponsor. This is true for external sponsors, such as Industry-Sponsors, as well as Sponsor-Investigators. Some external sponsors provide investigators with a draft budget to work from, whereas others request that investigators draft a budget themselves. In the event that an external sponsor provides the draft budget, it usually comes as a part of the [Draft Clinical Research Agreement](#).

Investigators who receive a draft agreement from an external sponsor should submit the documents to the [corresponding contract and budget management office](#) for negotiations. Appropriate personnel at these offices will evaluate the draft budget and provide advice and recommendations to ensure that the budget meets the investigator's and institution's needs. Investigators are consulted to ensure that appropriate fees are considered during this process.

Budget Building Blocks

Negotiating a clinical research budget begins with a review of the protocol's schedule of events (also referred to as *Visits and Procedures*). Proper scrutiny of procedures, location of said procedures (labs, exam rooms, etc.), and time and effort should be performed (professional charges and technical fees must be taken into account). Then, a coverage analysis of standard of care versus research should be performed for the procedures detailed in the schedule of events. This information is then compared with the numbers provided in the draft budget and adjusted accordingly. This process should be performed by the appropriate [research administrative personnel](#) and the investigator together. It is important to review these costs in conjunction, as both parties provide forms expertise that is necessary to identifying appropriate costs. Proposed changes to the draft budget are based on the Research Fee Schedule:

- [The Biomedical Research Alliance of New York](#) manages this process with investigators of Industry-sponsored

- [The Office of Clinical Trials](#) manages this process for Investigator-Initiated trials (including Investigator-Initiated Industry Sponsored Trials)
- [The Office of Research Sponsored Programs](#) manages this process for all government funded research projects with grants that will be awarded to Montefiore Medical Center.
- [The Office of Grant Support](#) manages this process for all government funded research projects with grants that will be awarded to Albert Einstein College of Medicine.

REGULATORY REQUIREMENTS

Clinical research is subject to several forms of regulation: Federal, state, local, and institutional. All research personnel are expected to be familiar with and abide by these regulations in their planning and conduct of clinical research.

Federal Regulations

Two governmental bodies provide regulatory oversight on clinical research conduct under the [U.S. Department of Health and Human Services \(HHS\)](#).

- The Office for Human Research Protections (OHRP)
- Food and Drug Administration (FDA)

The Office for Human Research Protections (OHRP) Regulations

[The Office for Human Research Protections \(OHRP\)](#) provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research. OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research.

[Code of Federal Regulations, Title 45 Part 46 \(45CFR46\)](#)

Basic regulations governing the protection of human subjects in research supported or conducted by the HHS and OHRP are found in the [Code of Federal Regulations Title 45 Part 46](#). This regulation establishes the standard of ethics for the conduct of government-funded biomedical and behavioral human subject research in the United States. Research personnel at Montefiore Medical Center and its affiliates are held to these guidelines, regardless of the research's funding source. Personnel involved in the conduct of clinical research are expected to understand all aspects of the regulation.

Regulation 45 CFR 46 consists of five sub-parts (A, B, C, D, and E) described below:

- **Subpart A** (aka *The Common Rule*) is the basic set of protections for all human subjects of research conducted or supported by HHS, and was revised in 1981 and 1991, with technical amendments made in 2005.
- **Subparts B, C, and D** provide added protections for specific vulnerable groups of subjects:
 - **Subpart B**, issued in 1975, and most recently revised in 2001, provides additional protections for pregnant women, human fetuses, and neonates involved in research.
 - **Subpart C**, issued in 1978, provides additional protections pertaining to biomedical and behavioral research involving prisoners as subjects.
 - **Subpart D**, issued in 1983, provides additional protections for children involved as subjects in research.
- **Subpart E**, issued in 2009, requires registration of institutional review boards (IRBs), which conduct review of human research studies conducted or supported by HHS.

Food and Drug Administration (FDA) Regulations

[The Food and Drug Administration \(FDA\)](#) is an HHS agency that regulates clinical investigations of products under its jurisdiction, such as drugs, biological products, and medical devices. FDA regulations are published as part of Chapter 21 of the Code of Federal Regulations, and the FDA's human subject protection regulations are in parts 50, 56, 312 and 812:

- [21 CFR part 50](#) describes consent requirements for drugs and devices
- [21 CFR part 56](#) describes the requirements for IRB review.

Research that is subject to [45CFR46](#) involving an FDA regulated product that does not meet the criteria for an Investigational New Drug (IND) Exemption or for which there is an active Investigational Device Exemption (IDE) is additionally subject to all aspects of 21 CFR 312 (drugs) or 21 CFR 812 (devices).

- [21 CFR 312](#) describes the requirements for an Investigational New Drug Application
- [21 CFR 812](#) describes the requirements for an Investigational Device Exemption

Code of Federal Regulations Title 21 Part 11 (commonly referred to as *Part 11*) establishes the FDA regulations on electronic records and electronic signatures (ERES). [21CFR11](#) defines the criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable and equivalent to paper records.

New York State Regulations

Section [79-1 of the New York Civil Rights Law \("Section 79-1"\)](#), enacted in 1996, prohibits any person from performing a Genetic Test on a Biological Sample taken from an individual without the prior written informed consent of such individual, except where such Genetic Test is for purposes of research or newborn testing conducted in accordance with applicable laws and

regulations or is court-ordered. Accordingly, before a laboratory conducts a Genetic Test, it is necessary that the patient give written informed consent to that test.

Institutional Review Boards Expectations

As per the [Code of Federal Regulations Title 21 Part 56](#), any clinical investigation which meets the criteria for prior FDA submission (as required in 21 CFR parts 312, 812, and 813) shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an Institutional Review Board (IRB). This is the case unless the clinical research meets criteria for exemption detailed in section 21CF56.104.

Outlined below are the steps and stages of IRB of documents of clinical research documents:

IRB Initial Review

Investigators must submit a final protocol, study advertising materials, Informed Consent Form templates, and any other required study documents and materials to an Institutional Review Board (IRB) for *Initial Review* prior to conducting any clinical research activity. Official IRB approval is required in order to commence study proceedings. Investigators at Montefiore Medical Center can submit to one of two local IRBs depending on the study sponsorship and funding source:

- **Biomedical Research Alliance of New York (BRANY) IRB:** PIs of [Industry-Sponsored](#) clinical research should submit their final protocols to the BRANY IRB. Please refer to the BRANY IRBs Policies and Procedures for submission instructions as well as guidance on timelines and the approval process.
- **Einstein Office of Human Research Affairs:** All other PIs conducting clinical research involving human subjects should submit final protocols to the Einstein IRB for review. PIs should refer to the [Einstein OHRA Policies and Procedures](#) for submission instructions as well as guidance on timelines and the approval process.

Investigators utilizing the BRANY IRB for their review of clinical trial protocols must also utilize [BRANY's contractual and budgetary management](#) services. All industry sponsored clinical trials are reviewed by the BRANY IRB, with the exception of [Investigator-Initiated](#) Industry Funded Trials and a few others.

Investigators utilizing the Einstein IRB for protocol review are permitted to submit protocols to the IRB in tandem with submission to their [corresponding contract and budget management office](#). However, the Einstein IRB will not approve the protocol before the [Clinical Research Agreement](#) is fully executed.

Some clinical research may be exempt from IRB review. In order to determine whether a trial is subject to IRB review, Investigators should refer to the [Einstein OHRA Exempt Categories](#). For more information on IRB, including policies, procedures, and getting started please visit the [Einstein Office of Human Research Affairs](#).

Continuing Review

In accordance with the Code of Federal Regulations Title 45 Part 46, both Einstein and BRANY IRBs have implemented policies and procedures to perform continuing review of research conducted at Montefiore Medical Center and its affiliates. Continuing Review allows the IRB to reassess the totality of the project approved during the Initial Review stage, and assure that, among other things, risks to subjects are being minimized and are still reasonable in relation to anticipated benefits, if any, to the subjects and the knowledge that is expected to result.

While a research project is ongoing, the IRB reviews and considers proposed changes to the research as they are received, including protocol and consent form amendments. They also periodically receive and review reports of unanticipated problems involving risks to subjects or others (hereinafter referred to as “unanticipated problems”) and other information about the research. An investigator’s corresponding IRB will determine the frequency of continuing review, and appropriate steps for submission.

Refer to the Einstein IRB’s Policies or BRANY IRB Policy further information regarding continuing review

Amendments

An amendment refers to any change to the protocol design, the informed consent document and/or procedure, or the advertisement/recruitment letter, from that originally approved by the IRB, regardless of how minor. Protocol amendments usually occur when the sponsor amends a clinical research protocol due to newly gathered information regarding deadline pressures, difficulty recruiting adequacy subjects, and complexity in protocol design to name a few. Investigators who receive protocol amendments must submit it to the corresponding IRB for review.

The Principal Investigator (PI) is responsible for obtaining written IRB approval for any proposed amendment to the protocol design, the informed consent document and/or procedure, or the advertisement/recruitment letter prior to its initiation, except in cases where changes are necessary to prevent apparent immediate harm to protocol subjects. In these emergent situations, the PI is responsible for promptly reporting these changes to the IRB.

Minor amendments to the study can generally be reviewed by *Expedited Review* and include:

- Administrative changes
- Minor consent form changes
- Minor changes to recruitment procedures, recruitment materials or submission of new recruitment materials to be used in accordance with approved recruitment methods
- Minor changes to study documents such as surveys, questionnaires or brochures

- New study documents to be distributed to or seen by subjects that are similar in substance to those previously approved
- Changes in payment to subjects or the amount subjects are paid or compensated that are not significant enough to affect the risk/benefit ratio of the study
- Decrease in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ratio of the study
- Editorial changes that clarify but do not alter the existing meaning of a document
- Addition of or changes in study personnel
- Addition of a new study site (in many but not all cases)
- Translations of materials already reviewed and approved by an IRB

Personnel should refer and adhere to the [corresponding IRB's](#) Amendment Policy for guidance.

*NOTE: *Contractual or budgetary* amendments should be submitted to the [corresponding contract and budget management office](#).

Progress Reports/Continuing Review

Per federal and institutional regulations, ongoing research must be re-reviewed by the IRB at intervals appropriate to the degree of risk, but at least once per year. This process is referred to *continuing review* or submitting a *Progress Report*. The continuing review process is to be as diligent as initial review to ensure human subject protections. Please refer to the appropriate IRB for their policy on progress reports/continuing review.

Research Misconduct

Research misconduct includes, but may not be limited to, fabrication, falsification or plagiarism in proposing, performing or reviewing research or reporting research results. Fabrication is making up data or results and recording or reporting them. Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record. Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

For more information on research misconduct, please refer to the [Montefiore and Einstein Policy on Research Misconduct](#).

Complaints

It is important to recognize when misconduct or serious deviation from regulatory and ethical standards in the conduct of clinical research. Unethical behavior fosters a breach of confidence among investigators and undermines the trust that research subjects and the general public should have in clinical research. Process to receive research-related complaints have been implemented in order to effectively and adequately address to instances of misconduct:

Subject Complaints

Subjects are encouraged to contact the IRB to discuss any complaints or concerns related to their participation in research. IRB contact information is included in every Informed Consent Form. This option is also explained to potential subjects during the Informed Consent Process.

Staff Complaints regarding Human Subjects Research

When investigators have complaints or concerns regarding human research protections they are encouraged to contact one of the IRB chairs or the [IRB Director](#).

Employees who have complaints or concerns regarding the human research protections program are encouraged to speak with the PI directing the investigation. In cases where that is not appropriate, or the resolution is not acceptable, employees are encouraged to contact the [IRB Director](#).

Complaints or concerns regarding other aspects of the research program at Montefiore Medical Center, such as concerns regarding research billing, should be directed to the Montefiore [Office of Compliance](#) or the IRB Director.

Any concerns regarding the confidentiality of patient health information that has been collected as part of a research project should be directed to the [Montefiore Privacy Officer](#).

Conflict of Interest (COI)

Potential conflicts of interest (COI) related to clinical research are inherent in that academic advancement and professional reputation are dependent on recognition through publishing and presentation of research results. When financial gain is also possible, an additional dimension for potential conflict emerges.

Research subjects are asked to trust that the researcher has considered their interests in suggesting entrance into a protocol; that risks have been minimized; and that the intervention or experimental course of treatment will be monitored carefully. This trust is violated if self-interest (conflict of interest) interferes with the professional judgments of the researcher.

The doctrine of informed consent requires that a potential research subject consider the risks, benefits, and alternatives to the proposed research intervention. They must be given all the information that would be reasonably relevant to their choice, including information about potential conflict of interest.

For more information on Einstein OHRA policy regarding COI, please visit [Policy on Disclosing Financial Conflicts of Interest to the IRB](#).

Forms Related to Conflicts of Interest

Sponsors require all Key Personnel on the local study team to complete forms related to conflict of interest before commencing trial activities. These forms include:

Financial Disclosure Form (FDF): For drug and device research conducted under IND or IDE, research sponsors are required to obtain a completed and up-to-date Financial Disclosure form from all key research personnel. The sponsor would provide this form.

Conflict of Interest Form (COI): For all studies, the IRB requires all key research personnel to complete a COI form. The form asks questions about financial and other types of potential conflicts. A completed COI form is required even if there is no outside funding for a study.

Investigators utilizing the Biomedical Research Alliance of New York's IRB can expect to submit COI forms to their office, as well. Please refer BRANY's policies and procedures for further guidance on COI submission.

Good Clinical Practice (GCP) Policy

All investigators and personnel directly involved in new and ongoing clinical studies that involve the testing of drugs or devices, including all FDA-registered studies as well as investigator-initiated protocols, are required to be complete Good Clinical Practices (GCP) training. This requirement applies to studies reviewed by both the Einstein IRB, and approved external IRBs (e.g. BRANY, NCI CIRB, etc.).

Effective January 1, 2015, all Montefiore, Einstein and PAGNY employees who participate in clinical research (including faculty investigators) must have certification of completion of GCP training in order to submit a protocol to the IRB for review and approval

Any of the programs below will qualify:

- [Collaborative Institutional Training Initiative \(CITI\)](#)
- [Academy of Physicians In Clinical Research \(APCR\)](#)
- [FDA Investigator Course](#)
- [TransCelerate Biopharma, Inc.](#) approved courses
- [National Institute of Allergy and Infectious Disease \(NIAID\) Program](#)
- GCP courses offered by [ACRP](#) or [SOCRA](#).

Please refer to the [Einstein OHRA's Good Clinical Practice Education Website](#) for more information and guidance on this policy.

Registration Requirements for Clinical Trial Protocols

Certain clinical trial protocols are required to be registered on the National Institutes of Health's (NIH) [ClinicalTrials.gov](#) website. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

The purpose of the protocol registration requirement is to share with the public information that has been accrued from their participation in clinical research, where it is available to guide decisions about patient care. Another goal of the registry is to allow investigators to make available information to a broad array of potential subjects and for patients to find potential research enrollment opportunities.

Industry sponsors typically manage this registration process. However, PIs of Investigator-Initiated Protocols must register their trial themselves. Please refer to the [Einstein OHRA Policy regarding the Registration of Clinical Trials](#).

The Centers for Medicare and Medical Services (CMS) requires that National Clinical Trial Number (NCT Number), obtained when the trial is registered on [ClinicalTrials.gov](#), be reported on all billing claims for items/services related to a qualifying clinical trial. Please review the [National Clinical Trial Numbers](#) section of these guidelines under [Research Billing Compliance](#) for further detail.

Regulatory Binders and Study Documentation

Good Clinical Practice (GCP) guidelines require that all clinical trial information is recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified throughout the life of the trial, and after the study has been closed out (See [ICH GCP E6 Section 8](#)). Additionally, investigators of clinical drug or device trials are expected to adhere to trial record keeping requirements outlined in the [Code of Federal Regulations Title 21 Part 312 Section 62 \(21CFR312.62\)](#).

Regulatory Binder

Also known as an *Essential Document Binder*, *Trial Center File*, or *Trial Master File*, the Regulatory Binder is a binder or group of binders composed of different sections related to the research project. The purpose of the regulatory binder is to maintain study document organization and demonstrate compliance with GCP standards and applicable regulatory requirements. The binder also allows sponsors, IRBs, and FDA authorities to evaluate the conduct of a trial and its data quality. Regulatory binders must be kept with the PI and/or Study Coordinator at the central research site within the institution.

When an external sponsor provides a Regulatory Binder

Industry sponsors typically provide a format for the organization of the regulatory binder, indicating what should be filed in each section. Use of the different sections may vary according to need and trial type. Investigators should compare the sections of the binders provided by the sponsor with the [Einstein OHRA Required Documentation for the Conduct of Research Involving Human Subjects Policy](#). It is the responsibility of the Principal Investigators to add any relevant sections that may be missing.

When an external sponsor is not providing a Regulatory Binder

In the event that an external sponsor does not provide a regulatory binder template, or if the research is Investigator-Initiated, Principal Investigators should follow the requirements of the [Einstein OHRA Required Documentation for the Conduct of Research Involving Human Subjects Policy](#). The policy lists the essential documents that should be filed in each section. This policy was developed to help study sites achieve and maintain regulatory compliance and adhere to high standards of practice in

the conduct of research involving human subjects, and is an especially useful resource for Sponsor Investigators conducting [Investigator-Initiated trials](#).

Investigators can customize their regulatory binder by including relevant sections and modifying the available logs and forms to conform to study specific needs. If more space is needed, investigators can divide the contents of the essential document binder across more than one binder. For more tips and guidance on building your own regulatory binder, please see the [Essential Document Binder Checklist](#) in Appendix A.

Within the Regulatory Binder

Investigators can find a table detailing the types of documents expected to be filed securely in the Regulatory Binder, and at which stage in the clinical trial process these will be obtained and stored in Appendix B. Follow these links to access this information:

- [Essential Documents : Before the Clinical Phase of the Trial Commences](#)
- [Essential Documents: During the Clinical Conduct of the Trial](#)
- [Essential Documents: After Completion or Termination of the Trial](#)

Ancillary Binders

Due to complexity, some clinical research studies require the establishment of additional binders that contain other pertinent documents, outside of those filed in the Regulatory Binder. Below are examples of the types of binders that can make up these Ancillary Binders:

Subject Binder

Investigators are expected to keep a subject binder for all clinical research participants in of the study. The subject binder should be kept and maintained by the PI and/or Study Coordinator at the central research site of the institution. Industry or federal sponsors sometimes provide research sites with a research subject binder template, which is sectioned and defines eligibility, procedures, visits, and all data to be captured. If a template is not provided by an external sponsor, the PI is responsible for creating the template.

In accordance with [21CFR312.62b](#), PIs of investigational drug and/or device trials are 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. Subject binders should be organized in a consistent manner so that research documentation is easily retrieved by any authorized individual that needs to access the information, regardless of the sponsor or funding source.

The subject binder should contain the following elements, among others: :

- Signed Informed Consent Forms

- Case report forms (CRFs)
- Pertinent Source Documentation
- IRB-approved study questionnaires
- Study Visit notes
- Study Logs
- Notes of Corrective Action (as applicable)

Investigational Test Article (Drug, Biologic, or Device) Accountability Binder

The Investigation Test Article binder should be kept either at the central site or where the Investigational Product (IP) is being dispensed, such as in the pharmacy where the study drug will be kept and dispensed. Industry or federal sponsors sometimes provide research sites with an Investigational Test Article Accountability Binder template, which is sectioned, for all documentation that is to be maintained. The binder should contain:

- Shipment and receipt records
- Randomization log (if applicable)
- Orders
- Central accountability log specific to the study's needs
- Record of dispensing
- Return/destruction records.

If a binder template is not provided by a sponsor, the PI is responsible for ensuring that a template for the investigational product is created.

Source Documents

Source documents are original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of clinical research data. It should enable an independent observer to reconfirm the data. Source Documents are required to be either within the research subject binder or in an inpatient or outpatient medical record.

The source data may be recorded by a member of the research team during a study visit, reported to the study team electronically (ex. imaging/lab reports) or represent a relevant clinical evaluation that may be planned or unplanned (ex ED Treatment Summary).

Examples of source documents include:

- Subject Questionnaires
- Imaging Reports
- Pathology Reports
- Records of Physical Exams
- Progress Notes

Source data are typically entered thereafter into a [Case Report Form \(CRF\)](#). Unless specified otherwise in the written research plan or protocol, each observation or data point entered into a CRF should have a corresponding source document.

The Study [Monitor](#) confirms that the data and observations recorded in the source documents are consistent with the data and observations entered in the case report form. This process is called monitoring, discussed further in the [Monitoring Visits](#) chapter. Any discrepancy between the source document and the case report form will result in a *query*, which is a written request for clarification.

Protocol Specific Source Documents

Protocol Specific Source Documents are forms specifically created to record data and observations for a specific study. Forms may be developed by a member of the study team or provided by the study sponsor. Forms are typically printed in advance of a research study visit, completed by hand during the visit, signed and dated. Industry sponsors typically design their own (protocol specific) source documents and provide them to a Principle Investigator.

Tips for Creating Protocol Specific Source Documents

- Headers on each page should be standardized
- Date/subject identifier should be included on each page
- Each data point should be attributable to the staff member who collected the data or made the observation (initialed/signed and/or dated at the bottom of each page or at the end of a group of related pages)
- Response fields should be placed in a consistent order on each source page

Quality source data is:

Accurate	Each observation or data point is accurately recorded.
Legible	Data is readable and recorded in a permanent medium, e.g. ink for written records or electronic records that are unalterable.
Contemporaneous	Data is recorded at the time the observation was made; if data is recorded at a later time, this should be clearly noted.
Original	Source data, by definition, is the place where the data or observation is first recorded, not a copy of observations found elsewhere in the record.
Attributable	Data should be traceable by signature and date to the individual who recorded it (or changed the entry after it was originally recorded).

Consent, Assent and HIPAA Authorization Forms

Original signed consent, assent and authorization forms are to be retained by the investigator. They may be kept with the subject source documents or a separate subject binder. Original signed consents should not be filed with the clinical medical record. However, a copy should be included in the subject's clinical medical record. A photocopy (or second signed original) must be provided to the subject. Investigators should refer to the [Einstein Office of Human Research Affairs Guidelines on the Informed Consent](#) process for guidance.

Case Report Forms (CRFs)

A Case Report Form (CRF) is a printed or electronic document designed to record all of the protocol-required data to be reported to the sponsor for each research subject. Typically, only information included in the planned data analysis is collected on the CRF. Infrequently, data may be entered directly onto a case report form and there will be no corresponding source document. This may occur when the subject completes a questionnaire that is also a case report form. If data is to be recorded directly on the CRF, this should be described in the IRB approved research plan.

Industry sponsors are responsible for the design and distribution of Case Report Forms. While sponsors do not always provide *protocol specific* source document forms, they always provide the CRFs that will be used to collect the study data. CRFs generally do not include any protected health information or identifying information about the subject.

CRFs may be "paper" or "electronic," also referred to as *eCRF*. Paper CRFs are binders filled with preprinted forms that the study site completes with data collected for each subject. When eCRFs are used, the site enters data into a database and the information is transmitted electronically to the Data Coordinating Center. This is also called *Remote Data Entry (RDE)* or *Remote Data Collection (RDC)*.

Sponsor-Investigators conducting Investigator-Initiated studies often have to develop their own Case Report Forms. These investigators can seek assistance with study design and CRF development through the Bioinformatics, Biostatistics, and Study Design Cores of the [Institute for Clinical and Translational Research](#).

Privacy and Confidentiality

Montefiore and Einstein are committed to ensuring the rights of research subjects with respect to the protecting the privacy of their health and research records.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The Health Insurance Portability and Accountability Act (HIPAA) protects the privacy of [individually identifiable health information](#). The HIPAA Privacy Rule provides federal protections for individually identifiable PHI held by [covered entities](#) and their business associates. It also grants patients several rights with respect to that information. On the

other hand, the Privacy Rule also permits the disclosure of health information that is needed for patient care and other important purposes, such as research needs.

Covered Entity

A Covered Entities are defined in the HIPAA regulations as (1) health plans, (2) health care clearinghouses, and (3) health care providers who electronically transmit any health information in connection with transactions for which HHS has adopted standards. Montefiore Medical Center is a covered entity.

Individually Identifiable Health Information

The Privacy Rule protects all “*individually identifiable health information*” held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper, or oral. The Privacy Rule calls this information “protected health information (PHI).”

“Individually identifiable health information” is information, including demographic data, that relates to:

- the individual’s past, present or future physical or mental health or condition,
- the provision of health care to the individual, or
- the past, present, or future payment for the provision of health care to the individual

More information on HIPAA, as it applies to research, can be found here:

<http://www.hhs.gov/ocr/privacy/hipaa/understanding/special/research/>
http://privacyruleandresearch.nih.gov/clin_research.asp

De-Identified Data

The Privacy Rule allows a covered entity to de-identify data by removing all 18 elements that could be used to identify the individual or the individual's relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual who is the subject of the information. Under this method, the identifiers that must be removed are the following:

1. Names.
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
3. Telephone numbers.
4. Facsimile numbers.
5. Electronic mail addresses.
6. Social security numbers.
7. Medical record numbers.
8. Health plan beneficiary numbers.
9. Account numbers.
10. Certificate/license numbers.
11. Vehicle identifiers and serial numbers, including license plate numbers.

- a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
 - b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
 13. Device identifiers and serial numbers.
 14. Web universal resource locators (URLs).
 15. Internet protocol (IP) address numbers.
 16. Biometric identifiers, including fingerprints and voiceprints.
 17. Full-face photographic images and any comparable images.
 18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Limited Data Set

A Limited Data Set is similar to a *de-identified data set* except that the following data elements are allowed: *zip code, city, and state, date of birth and other dates*. If a limited data set is to be used, a *Data-Use Agreement* is required. Contact [The Office of Clinical Trials](#) for guidance on establishing a Data-Use Agreement.

Coded Data

Coded Data (Linked Data) are separated from personal identifiers through use of a code. Coding involves classifying information implemented to facilitate data analysis both quantitatively (questionnaire results) and qualitatively (interview transcripts). Coding transforms research data into a form understandable by computer statistical software. One code should apply to only one category and categories should be comprehensive. There should be clear guidelines for coders (individual who do the coding) so that code is consistent. Some studies will employ multiple coders working independently on the same data. This minimizes the chance of errors from coding and increases the reliability of data. As long as a link to PHI exists, data are considered indirectly identifiable and not anonymous or anonymized.

Double Coded Data

Double-coded data are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. In general, Principal Investigator is responsible for maintaining the first coding key and does not have access to the second coding key.

Anonymized Data

Anonymous Data is collected without identifiers and that were never linked to an individual. Coded data are not anonymous. Anonymized data is previously identifiable data that have been de-identified and for which a code or other link no longer exists. An investigator would not be able to link anonymized information back to a specific individual.

Investigators who require assistance with study design and data set management should contact the [BERD](#) and [RIC](#) Cores of the [Institute for Clinical and Translational Research ICTR](#). Any questions regarding data privacy and its intended use in a clinical research study should be directed to the appropriate [Institutional Review Board \(IRB\)](#).

STUDY MANAGEMENT

The following chapter describes a typical sequence of events for active clinical research studies at Montefiore Medical Center (MMC) and its affiliates. Some information is particular to clinical trial research, while others are more generally applicable.

Study Activation

In order for a clinical research study to begin, official IRB approval must be granted and a clinical research agreement must be fully executed. Investigators may be given official notice from their corresponding contract management office (OCT, BRANY, ORSP, Grant Support) in the form of an Activation Letter, stating that contracts have been signed by all appropriate signatories. Investigators should contact the [corresponding contract management office](#) for guidance. Additionally, PIs of industry sponsored clinical trials will usually receive a Site Initiation Letter, stating that research activity may begin as long as IRB approval has been given. This Site Initiation Letter usually follows the completion of a successful [Site Initiation Visit \(SIV\)](#).

Regardless of study sponsorship and funding, PIs should have established a strategy for how the study will be executed and patients recruited at the site by the time of Study Activation.

Site Initiation Visits (SIV)

Once an investigator receives IRB approval, the sponsor may conduct a Site Initiation Visit (SIV). During the SIV, sponsors will typically train the local study team on the trial procedures and expectations. The PI and Study Coordinator are responsible for ensuring that all appropriate study personnel are present during this visit. At the end of the SIV, the PI will usually receive a Site Activation Letter or notice, after which point, he/she may officially commence clinical research activities.

Device Certification and Bioengineering

Studies involving the use of investigational devices must have the investigational device certified by Montefiore Medical Center's Bioengineering Department. Investigators must contact

Bioengineering at 718-920-4265 prior to having the investigational device shipped to the institution. Investigators should follow the processes outlined by the Bioengineering Department. No Investigational Device should be on institutional grounds without receiving certification and approval from the Bioengineering Department.

Pre-Screening and Identifying Potential Trial Participants

A successful clinical research outcome depends on subject enrollment rates. Study teams that have realistic enrollment expectations prior to beginning a study, and who prepare strategies for subject identification and recruitment will likely have higher enrollment rates. The following sections describe typical pre-screening and recruitment processes.

Pre-Screening

Pre-Screening is a process used to determine a patient's initial eligibility for and interest in a study. It is common practice for many clinical research studies; some may even require a Pre-Screening Study Visit as part of the research protocol. Pre-Screening may save investigators time by quickly identifying subjects who may qualify for a study, prior to moving the patient on to the informed consent process. Investigators may pre-screen a patient by:

- Reviewing a patient's chart for eligibility
- Talking to patients in person within an investigator's clinic
- Discussing the study with a patient over the phone

Identification of Potential Research Subjects Using Medical Records

Prior permission must be obtained from a patient in order to contact him or her about a study via private medical record information/database. Investigators should review and adhere to the [Einstein OHRA Use of Protected Health Information \(PHI\) in Research](#) before contacting patients for Pre-Screening purposes.

IRB approval of a HIPAA waiver is required to prescreen Montefiore medical records to identify potential participants for a clinical trial. An investigator, who has requested and received an IRB HIPAA waiver for activities preparatory to the trial, may review medical records for the purpose of pre-screening (identification of potential participants). Medical records may include clinic appointment lists, Operating Room (OR) schedules and individual medical records.

If the investigator does not have a treatment relationship with the subject, and medical records are used to identify the individual as a possible participant, a member of the treatment team must make the initial contact with the patient. Refer and adhere to the Einstein OHRA Policy for [Einstein OHRA Use of Protected Health Information \(PHI\) in Research](#).

NOTE: Patients who call the study team in response to an IRB approved advertisement have given implicit permission.

Private Health Information and Recruitment

Individually identifiable health information may include common identifiers such as name, address, birth date, medical record number and Social Security Number. "Protected Health Information" (PHI) is any information, including demographic data, which relates to:

- The individual's past, present or future physical or mental health or condition,
- The provision of health care to the individual, or
- The past, present, or future payment for the provision of health care to the individual.

Recruitment

If the investigator does not have a treatment relationship with the subject, and medical records are used to identify the individual as a possible participant, a member of the treatment team must contact the patient by mail, phone or briefly describes the study during an office visit. If the patient indicates that they wish to learn more about the study, the researcher may contact the potential subject. If the patient is not interested in learning more, the researcher may not contact the individual.

If the Montefiore medical record has been used to identify potential subjects, any letter regarding the study must be authorized, signed and sent to the patient by a member of the patient's treatment team. If Montefiore medical records were not used to identify potential subjects (e.g.: mass-mailings), letters may be written, signed and sent by the researcher. Patients who respond to advertisements or recruitment letters have implicitly given their permission to be contacted. In all cases, letters sent to patients or potential participants regarding a research study must have proper IRB approval.

Recruitment Resources

There are several avenues to assist a clinical research team with recruitment efforts. Some are listed below:

[The Office of Clinical Trials](#)

Research teams may contact the OCT for guidance and best practices for recruiting subjects into industry-sponsored investigational drug and/or device trials. Investigators may review the [OCT's Research Subject Recruitment Brochure](#) for more information.

Physician, colleague, resident and fellow referrals

Investigators may ask colleagues to refer patients who may be potential participants for a study. No IRB approval is needed for letters sent to other providers to inform them about the study. Any printed information to be shared with a patient or potential participant must be reviewed and approved in advance by the IRB.

A popular recruitment method is to post a summary of your study for clinicians and department residents. Include a brief description of the study, as well as contact information for the study's coordinator and the most relevant inclusion and exclusion criteria. These posts can be updated and reposted weekly depending on the offices in which you have permission to post them and your target patient populations.

Because these postings are for clinician and resident reference only, they will require IRB-approval. However, be sure to keep these posts accurate, concise and eye-catching (e.g., print them on brightly colored paper)

External study sponsor

Investigators should contact study sponsors about best practices that have improved recruitment rates at other sites.

Electronic resources for event information

- Montefiore Update emails (Contact MMC Marketing Dept.)
- Montefiore intranet events calendar (Contact MMC Marketing Dept.)
- [Norwood News](#)
- [Bronx Times Events section](#)
- [Bronx Times Events Calendar](#)
- [Riverdale Press Events Calendar](#)
- [Bronx Penny Pincher Events section](#)
- Links to specific Bronx neighborhoods at the [Bronx News website](#)
- [American Towns](#)
- [The Bronx Tourism Council](#)
- [Eventbrite](#)
- [Bronx Mall](#)

Websites for clinical trial posts and recruitment

- [Center Watch](#)
Center Watch hosts one of the largest online databases of clinical trials that are actively seeking patients. You can post IRB-approved ads and descriptions of your studies, which prospective participants may search by medical condition, therapeutic area and location. To post your trial on this site, please send an email to OCT@montefiore.org.
- [ResearchMatch](#)
ResearchMatch is an online recruitment resource that is designed to match two groups of people: ResearchMatch Volunteers (individuals who wish to learn about studies in which they may participate) and ResearchMatch Researchers (those who register their studies with the ResearchMatch site). For more information about posting your trial on this site, please send an email to OCT@montefiore.org.

Advertisements

All advertisements for a clinical research study should be approved by the appropriate local IRB. Please review the [Einstein OHRA Recruitment/Advertisement Policy](#) for guidance.

Screening, Enrollment, and Ongoing Study Visits

Patients who have signed the ICF may continue onto the *Screening Visit*. At this visit, the PI conducts specific procedures dictated by the study protocol and intended to verify a patient's eligibility for study participation. Depending on protocol design, a patient who passes the screening visit may move on to the *Enrollment* (or *Randomization* if applicable) phase of a study. Patients who do not pass the Screening Visit are considered *Screen Failures* and are not exposed to further study procedures. Enrolled patients proceed through the study according to the clinical research protocol.

Some protocols may not require a Screening or Enrollment Visit. Screening visits are most common in investigational drug or device studies. Investigators are expected to adhere to the schedule of events detailed in their protocols when navigating a patient through the study.

Transportation

Some studies include transportation for research subjects in their design. Investigators who plan to provide transportation services for their subjects should review and adhere to the [Einstein OHRA Transportation of Subjects Policy](#).

Consenting

Once a potential research subject has been identified and has agreed to participate in the study, a PI must conduct the *Informed Consent Process* prior to commencing any study procedures. Informed consent involves an exchange of education and information that takes place between the researcher and the potential subject and is documented when the patient and investigator sign the *Informed Consent Form (ICF)*. During this stage, the PI should:

- Review the Informed Consent and HIPAA Forms with the patient in detail
- Explain all study procedures to the patient
- Answer any and all questions/concerns raised by the patient
- Give the patient adequate time to review the ICF and HIPAA Form should the patient so requests.
- Obtain ICF signature from the patient once the patient expresses full comprehension and interest in participation; the investigator or appropriate research personnel should sign the ICF after the patient.
- Give the patient a copy of the signed ICF, and file the original copy according to the IRB and Sponsor's requirements
- Reiterate next steps to the patient: Commence study screening procedures and/or schedule appropriate time for the next study visit

Investigators must adhere to the [OHRA's Guidelines on Informed Consent](#). These guidelines are based on accepted ethical principles, Federal Regulation and New York State Law. For more information on informed consent, please review the [FDA's Guide to Informed Consent - Information Sheet](#) for research involving FDA regulated drugs or devices.

Obtaining Consent for Research – Special Circumstances

Clinical research personnel may encounter special circumstances during the recruitment process that require additional measures for proper consenting. Listed below are examples of special circumstances:

Non-English-Speaking Participants

The written informed consent document must be in language understandable to the subject. Ideally, subjects who do not speak English should be presented with a fully translated consent document written in a language that is understandable to them. As the Bronx has a large Spanish speaking population, it is expected that Spanish speaking potential participants will be encountered. The Einstein IRB generally requires Spanish translations of consent documents for studies that plan to enroll 5 or more subjects with a potential for direct benefit to the participants. Studies providing an adequate scientific justification precluding Spanish translation may have the requirement waived.

If a potential participant is encountered who speaks neither Spanish nor English, and it is not possible to obtain a fully translated consent form in the individual's language, the oral presentation of informed consent information is permitted. The presentation is documented with a short form written consent document in the language understandable to the subject (stating that the elements of consent have been presented orally) and a written summary of what is presented orally.

Please contact the Einstein Office of Human Research Affairs to request a translated Short Form or guidance regarding how they are used. Review the [Einstein OHRA's Informed Consent Guideline](#) for Guidance.

Illiterate Participants and Participants Unable to Sign their Name

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. Investigators should refer and adhere to the [Einstein OHRA's Informed Consent Guidelines](#) for more information.

Vulnerable Populations and Related Topics

Children are considered a vulnerable population and per Federal Regulations described in the Einstein OHRA's [Enrollment of Children in Research](#), all research involving children is placed in one of four categories:

- Research not involving greater than minimal risk.

- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
- Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

At Montefiore Medical Center, when a research project proposes the inclusion of children as subjects, the Pediatric Protocol Review Committee (PPRC) must review and approve the research prior to IRB review. Contact the Chair of Pediatrics for information. For more information on children in research please visit [OHRPs FAQs on Research with Children](#) and the Einstein OHRA's guidelines on the [Enrollment of Children in Research](#).

Please review the Einstein OHRA Policies on other vulnerable populations in clinical research:

[Enrollment of Subjects in Significant Pain](#)
[Pregnant Women, Fetuses or Neonates Research Policy](#)
[Research Involving Psychiatric In-Patients](#)

Assent

Assent by children of appropriate age and maturity is mandated by [45 CFR 46.408](#) and the Einstein OHRA. Parents or legal guardians are authorized to grant permission for their minor children to be enrolled in research by completion of a consent form. Informing, empowering, and showing respect for children can be served by obtaining their *assent, or agreement*, to participate in research. Whoever is legally permitted to grant permission will be permitted to sign the HIPAA Authorization Form.

- Children ages 7-12, cognitively and developmentally capable of assenting, are required to sign a separate child assent form. This assent form is in addition to the Informed Consent Document (ICD) that the parent or legal guardian is required to sign.
- Children ages 13-17, cognitively and developmentally capable of assenting, may sign the same consent document as the parent or legal guardian.
- If a child is encountered that cannot understand/sign the assent due to physical, developmental or cognitive issues, and consent has been obtained from the parent, this should be documented in the research notes.
- Children turning 7 should sign an assent to continue in a study, children turning 13 should have their assent documented on same document as their parent and those turning 18 must sign an adult individual consent form to continue. The parent's consent is no longer valid after a child turns 18.
- If the minor is the parent of a child or has married, parental permission is generally not required, and the minor may grant his or her informed consent. The

minor should be assessed to ensure he/she has the capacity to weigh the benefits, risks, alternatives and other required elements of informed consent.

Investigators should refer to the [Einstein OHRA Informed Consent Guidelines](#).

Good Clinical Practice

Study Personnel are expected to remain compliant with the [Einstein OHRA GCP Education policy](#) throughout the lifetime of the study. Key Study Personnel must complete further training if and when GCP certification expires during the lifetime of a clinical research study.

Data Collection and Entry

Clinical research studies conducted at Montefiore Medical Center and its affiliates typically require at least two forms of data entry. As study activity takes place, the appropriate research personnel (usually the Study Coordinator) captures the relevant clinical research data in the appropriate data capture systems accordingly. Investigators are expected to adhere to these requirements throughout the life of a clinical research protocol. Investigators are also expected to capture the study visit in MMC's Electronic Medical Record (EMR) system, and adhere to the [Research Billing Compliance Policy](#) regarding study and clinical Standard of Care (SOC) procedures.

External Sponsor's Data Capture System

Many sponsors require local study teams to record data into protocol specific [Case Report Forms \(CRF or e-CRF\)](#) usually housed in an Electronic Data Capture (EDC) system. Investigators should adhere to sponsor's requirements for data entry.

Institutional Clinical Trial Management System (CTMS)

Montefiore Medical Center utilizes an internal *Clinical Trial Management System (CTMS)* track and account for the clinical research activity taking place at MMC and its affiliates. A CTMS allows for storage and organization of relevant electronic study documents, scheduling and tracking of research subject study appointments, and administration of study finances. Study coordinators are required to record relevant research subject data as dictated by [The Office of Clinical Trials](#), into the appropriate CTMS software monthly. Please contact the OCT for the most updated information regarding the institutional CTMS.

Biomedical Research Alliance of New York's (BRANY) SMART System

Investigators with industry-sponsored clinical trials managed by [The Biomedical Research Alliance of New York \(BRANY\)](#) must utilize BRANY's SMART system and adhere to their data entry requirements. Study Coordinators should contact BRANY for SMART Guidance.

Data Safety Monitoring

Monitoring is the collection, review, and analysis of data as the clinical research study progresses to ensure the appropriateness of the research, its design, and subject protections.

Federal regulations require the local IRB to determine that, “when applicable, the research plan makes adequate provisions for monitoring the data collected to ensure the safety of subjects.” (45 CFR 46.111(a)). A Data Safety Monitoring Plan (DSMP) serves to protect the safety of participants and ensure the integrity of the data. All studies involving human subjects require some level of data and safety monitoring.

The study sponsor is responsible for ensuring that the DSMP is executed as described in the research plan. If the research is investigator-initiated and there is no external study sponsor, the Investigator is responsible for ensuring that the DSMP is executed as described in the research plan or protocol. The intensity and frequency of monitoring should be tailored to fit the expected risk level, complexity and size of the particular study. Monitoring can take several forms depending on the type of clinical research and sponsorship.

Examples of Data Safety Monitoring Plans:

PI Monitoring

For some studies, the PI will be the monitoring entity. This type of monitoring may be appropriate when the study is investigator-initiated, the study involves a small number of subjects, the study is conducted only at one site, and the range of possible study events that could have an important impact on the risks to research participants is narrow. In such cases, continuous monitoring of events by the PI and prompt reporting of unanticipated problems to the IRB, and FDA or others as appropriate may be adequate.

Monitoring by a Data and Safety Monitoring Committee (DSMC)

A Data and Safety Monitoring Committee (DSMC) is a group of qualified and objective individuals not directly involved with the design and conduct of the study. The members of a DSMC are typically recruited from within the Institution. The names and qualifications of the experts should be provided to the IRB at the time of protocol review.

This type of monitoring may be appropriate when the study is investigator-initiated, involves large numbers of research participants, particularly vulnerable populations, multiple performance sites, blinded study groups, particularly high-risk interventions or when sophisticated data monitoring/statistical analysis is required.

Monitoring by a Data and Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) is similar to a DSMC but the members are typically external to the research institution. A DSMB may be appropriate when the investigation involves an external sponsor such as a drug or device company. Investigators should review the [Einstein OHRA Data and Safety Monitoring Policy](#) for further information.

Data Validation

Clinical research often requires a data validation process, in which clinical data collected at the local site level is centrally reviewed, integrated, and statically analyzed by the sponsor. This is an especially important step within investigational drug and device trials. Data validation confirms the data's integrity and ensures confidence in the study's results and conclusions that are publicly made about the safety, tolerability, and efficacy of the investigational product.

Data validation is a process involving several layers of confirming the accuracy of the data:

- Monitoring
- Data Queries
- Database Lock

Monitoring

Sponsors must ensure that studies are adequately monitored. Monitoring (also called *Site Data Verification*) is the act of confirming that source data are collected and recorded properly, and that the study is being conducted according to applicable Standard Operating Procedures (SOPs) and regulatory requirements. Monitors meet periodically with research coordinators and investigators to review study records. Monitors do not interact with subjects; they interact solely with study personnel.

The sponsor usually determines the appropriate extent and nature of monitoring prior to launching a study at the local site. The determination of the extent and nature of monitoring is based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. Sponsors often commit to 100% Source Data Verification (100% SDV). This means that every data point recorded in the [case report forms \(CRF\)](#) will be confirmed by the study monitor to be consistent with the data recorded in the corresponding [source document](#).

If there is no external study sponsor (investigator-initiated research), it is the investigator's responsibility to verify that data has been collected and recorded accurately. For more information on the typical sequence events of study monitoring, please review the [Monitoring Visits](#) subsection of this document.

Queries

After the source documents are monitored, the data is submitted to a data coordinating center for review. This central review process is considered to be the actual Data Validation process. While efficient and responsible monitoring should detect most data discrepancies prior to the Data Validation stage, it is possible that discrepancies will be noted after the CRFs are transmitted to the data center. For example, an adverse event may have been recorded without a start or end date. The data coordinating center usually then issues a written *query* (also called a Data Clarification Form or DCF) with a request that the data be revised or clarified. The query is usually made to the study coordinator, although the PI is ultimately responsible for ensuring the data query is resolved.

The original data entry should not be removed or otherwise obliterated when attempting to resolve the data query. The site should request guidance from the study monitor as to how the correction should be recorded.

Database Lock

A database Lock (DBL) is an action taken by the sponsor to prevent further changes to a clinical research database. A database lock occurs when all study data have been reviewed, queries resolved, and issues addressed. Study sponsors will indicate to the local study team when they can expect a database lock and whether there are any specific steps that should be taken. At this stage, the local study team will not be permitted to enter or change study data in the designated eCRF/data capture system for the study.

Monitoring Visits

Investigators of externally sponsored clinical research studies can expect to host several monitoring visits required by the study sponsor. Sponsors and/or CROs usually develop monitoring plans that includes the frequency and duration of periodic [Site Monitor](#) visits at the beginning of the study. Typically, at these visits, a sponsor/CRO will evaluate the way the study is being conducted at the site and perform source document verification.

These monitoring visits vary in frequency - they can occur every few weeks to once a year and can last anywhere from a couple of hours to several days at a time. Information regarding the frequency, duration, and data entry expectations of a sponsor's monitoring visit can usually be found in the Clinical Research Agreement (CRA/CTA). The Study Coordinator should take care to schedule the visits.

Preparing for Sponsor's Periodic Monitoring Visits:

- Identify a quiet place for the monitor to work and ensure access to a copy machine, phone, water fountain, and restroom
 - Monitor should have their own workspace separate from the research study team
 - Set up Internet Access for monitor
 - Register Monitor in *Vendor Mate System* (review Montefiore's [Vendor Credentialing and Access Policy](#) and [Medical Vendor Representatives Policy](#)) and ensure all HIM/eHIT security clearance requirements have been met. This letter details the process for the vendor.
- Complete all necessary CRFs
- Confirm that applicable AE and/or SAE forms have been submitted and are available for review
- Obtain medical records for the CRFs to be reviewed (ensure that HIM requirements have been met)
- Organize study file documents for review
- Confirm that signed consent forms for all enrolled participants are available
- Schedule an appointment for the monitor to visit the pharmacy if needed

- Schedule time for the investigator to meet with the monitor towards the end of the visit to review findings

Note: The Pre-Site Selection (PSSV) and Site Initiation Visit (SIV) are also considered “Monitoring Visits.” Investigators can use the tips above to prepare for these visits as well.

Audits and Inspections

Like monitoring visits, *Audits* are intended to ensure quality in the conduct of a clinical research study at a given site. More specifically, an audit is a systematic and independent examination of the study related activities and documents. The purpose of an audit is to determine that a clinical study has been performed in compliance with the protocol, FDA, and/or other government regulations. Audits can be performed by the Food and Drug Administration (for Investigational Drug or Device Trials), study sponsors, or a local IRB.

FDA Audits (for Investigational Drug/Device Trials)

FDA audits, often referred to as **inspections**, usually occur after a drug or device trial has been completed. They can also occur *during* a trial in the event that a monitoring visit reveals a compliance problem. FDA auditors review study data against source documents, drug accountability, and the completion of all required documents, as well as relevant site facilities. Visits from the FDA may be scheduled or unscheduled. An unscheduled FDA audit usually occurs when the FDA believes there is a failure to meet regulatory requirements, and illegal activity may be occurring.

There are two types of FDA Inspections:

1. Routine Inspections
2. Directed or “For Cause” Inspections

Routine Inspections

Routine Inspections are assigned for New Drug Applications (NDA) and are conducted for studies that are crucial to a product’s evaluation and approval. Sites are selected randomly on a percentage of all clinical data submitted with applications for new products. It is generally believed, however, that clinical investigators who enroll the most patients in the NDA’s pivotal trials are the most likely candidates for a routine inspection.

For - Cause Inspections

For - Cause Inspections are conducted when the FDA has a specific reason for inspecting the site. Reasons can include:

- PI has participated in a large number of trials
- PI has performed work outside his/her specialty
- The safety or efficacy results are inconsistent with those of other sites conducting the same study
- The PI claims too many subjects with a specific disease or indication compared with the low numbers associated with his/her practice
- Complaints of alleged violations of the regulations, protocol, or human rights

have been filed by a patient or sponsor

Steps prior to a FDA Inspection

1. PI receives an audit notification letter from the FDA
2. Coordinator schedules a time for Sponsor to review/organize study documents with study team
3. Coordinator and PI notify the following institutional offices and personnel of the impending FDA audit:
 - IRB
 - Department Chair
 - Research Administrators
 - Research Billing Compliance
 - Compliance
 - Pharmacy

If applicable, also contact the following:

- Medical Records Department
 - Medical records department
 - Technical departments (ECG, x-ray)
 - Laboratory
 - Clinical Research Center (CRC)
4. FDA investigator contacts the PI (usually 2-3 weeks in advance) to schedule the inspection.
(Note: The FDA may show up unannounced In a **For-Cause Inspection**)
 5. Coordinator reserves a private workspace in advance for the inspector. The room should have access to a telephone, and wireless internet access.
 6. Coordinator and PI conduct a thorough review of all study related documents prior to the audit. Sponsor/CRO will usually review study documents as well during their visit.

Prepare the following records prior to the inspector's arrival:

- All study documents that were requested by the inspector
- All versions of the original signed ICF for all subjects including Screen Failures
- Completed (e)CRF's
- Source documents, subject charts, medical records, and lab reports
- All versions of the protocol, amendments and Investigator Brochure (IB)
- All IRB submissions and approvals
- All drug receipt records, dispensing records and return records
- Complete and current Regulatory Binder
- Appointment calendar
- Delegation of Authority Logs

- Sponsor and CRO correspondence and newsletters
- Certification of service /calibration of study-related equipment
- Laboratory certification and normal values
- Departmental Research SOPs and all relevant policies

Investigators are obligated to provide such relevant records in accordance with the [Code of Federal Regulations 21 CFR 312.68](#)

During the Inspection

During the audit, the Inspector compares the data submitted to the trial sponsor via the given data capture system, with medical charts and source documents supporting the data. The latter can include medical charts, laboratory reports, the drug accountability logs, pharmacy records, and similar study documents. Inspectors may review data pertaining to particular subjects from both before and after study participation. The purpose of this type of review is to ensure the subjects meet all inclusion and exclusion criteria for the study. Generally, inspectors choose to review only a subset of the study data. However, an inspector may choose to review more as he/she deems necessary. This is especially the case, if problems are encountered within the initial review of the data subset.

At the end of the audit, the inspector usually meets with the PI to review and discuss any findings. Any discrepancies and/or violations encountered are documented on FDA Form 483, which is then given to the Sponsor and the PI.

Tips for Investigators during an FDA Inspection

- Use the same room throughout the audit
- Provide ONLY requested materials
- Ensure there are no records pertaining to any other clinical trials in the room
- Have a designated contact person who can address questions, provide administrative support, and fulfill all requests from the auditor including making photocopies.
- Document all records requested by the auditor
- Document all questions asked by the auditor and who answered them
- Ensure the auditor is escorted at all times by site personnel

See the [Investigational Site Inspection Checklist](#) for more guidance.

Post Inspection - Consequences

After the inspection, the FDA Inspector writes an Establishment Inspection Report (EIR), which he/she submits to FDA Headquarters for evaluation. The PI should expect a letter, which can detail one of three possible scenarios.

1. The letter is an acknowledgement that the inspection has been completed and no significant deficiencies have been found.

2. The letter lists the deficiencies noted during the investigation but indicate that no specific response is necessary. However, the investigator should take voluntary steps to correct and improve this situation as these areas will be the focus of the next investigation.
3. The letter describes serious negative findings identified by the inspector. Indicating that the PI's status and validity of the collected study data are in serious jeopardy. An immediate detailed response is required to explain how these discrepancies will be addressed. Investigators who receive this type of letter should inform the study sponsor immediately.

Failure to adequately respond to this letter can result in the PI being disqualified from conducting other studies, rejection of the study data and perhaps the entire marketing application, and even potential criminal proceedings. Those investigators referred for criminal prosecution are generally clinical investigators who have knowingly or willingly submitted false information to a research sponsor.

The PI may request the EIR within four to six months of the inspection. In accordance with the Freedom of Information Act, EIR is available to the sponsor, and the general public (including other potential study sponsors). Sponsors and Contract Research Organizations (CRO's) routinely obtain this information when evaluating potential research sites. While it a noted discrepancy does not necessarily indicate a site will be passed over for future studies, potential sponsors will expect PIs and sites to demonstrate that a particular discrepancy has been address and have implemented processes to prevent future recurrences.

Sponsor Audit

Study sponsors may initiate an audit on their own clinical study activity at the research site in order to ensure quality assurance. These audits are different from their [Monitoring Visits](#). Sponsor's intent with an audit is generally to evaluate compliance with recognized standards, such as the FDA's Code of Federal Regulations, International Conference on Harmonization, International Standards Organization and Standard Operating Procedures. Sponsor-initiated audits provide further oversight of their clinical research study than monitoring alone, and functions as a safety net to catch potential mistakes or lapses on the part of the study monitor.

Sponsors usually hire an independent organization to conduct their audits. Audits are not performed continuously, the way that monitoring is performed during a study, but instead are compliance snapshots in time. In addition, audits are not required by U.S. regulations, but are voluntarily performed with the intention of preventing an [FDA Audit](#).

Below is a table detailing the ways in which sponsor audits differ from monitoring.

Monitoring vs. Auditing

	Monitoring	Auditing
Definition	Act of overseeing the progress of a clinical trial	Systematic and independent examination of the trial related activities and documents
What's Reviewed	100% source document verification of all participants	Snapshot in time of a subset of participants
Purpose	<p>Ensuring that the study is conducted, recorded and reported in accordance with:</p> <ul style="list-style-type: none"> • Protocol • SOPs • GCPs • All applicable regulatory requirements <p>Each protocol will outline a data safety and monitoring process and plan</p> <p>Some studies may require a data safety monitoring board/committee (DSMB/DSMC)</p>	<p>Determine whether the trial related activities were conducted and data recorded accurately, analyzed and appropriately reported according to:</p> <ul style="list-style-type: none"> • Protocol • Sponsor's SOPs • GCP • All applicable regulatory requirements

IRB Audit

The Einstein OHRA can audit clinical studies taking place at Montefiore or its affiliates to ensure subject safety. Investigators can request the assistance of the IRB to audit their studies in preparation for or to prevent a sponsor or FDA audit if applicable. For information on Einstein OHRA auditing policies please review their [Audit and Inspection Guidelines](#) and [Audit Policy](#).

BRANY's IRB conducts monitoring and auditing services for clinical trials. For more information on BRANY's auditing process please review their [Monitoring and Auditing Services](#) page.

Patient Safety Reporting

During the conduct of clinical research, events may occur that involve risk or injury to the participants or complications while they are a research subject. It is important to monitor these events in order to ensure the immediate safety of research subjects, and because they may warrant consideration of substantive changes in the research protocol, or informed consent process/document, or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

Montefiore Medical Center has implemented policies for reporting and managing these occurrences. These events can be characterized as *Adverse Events* and/or *Unanticipated Problems*. Principal Investigators are expected to maintain logs of all the Adverse Events or Unanticipated Problems that occur and may require submission to the IRB as per Einstein or BRANY IRB Policy.

Below is a description of the AEs, SAEs, and UPs:

Adverse Events (AE)

An *Adverse Event* (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. AEs encompass both physical and/or psychological harms. An adverse event can arise from any use of study drug (e.g. off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

For multi-centered clinical research trials, adverse events can be characterized as either *internal* or *external*. From the perspective of one particular institution engaged in a multicenter study, internal adverse events are those AEs experienced by subjects enrolled by the investigator(s) at that particular institution, whereas external AEs are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the same study. In the context of a single-center clinical study, all AEs would be considered internal adverse events as there are no other patient enrolling sites involved in the research.

Unanticipated Problems (UPs)

An Unanticipated Problem (UP) is any event, deviation, or problem that meets **ALL** of the following criteria:

- is unexpected; AND
- is possibly, probably or definitely related to study participation; AND
- is fatal, life-threatening, or serious OR suggests greater risk of harm to study participant(s) or others than was previously known or recognized.

Unexpected

An event can be categorized as *unexpected* if it occurs in one or more subjects participating in a research protocol; and the nature, severity, or frequency of the event is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in protocol-related documents such as: the IRB-approved research protocol; any applicable investigator brochure; the

current IRB-approved informed consent document; or other relevant sources of information, such as product labeling and package inserts; OR

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Serious

An adverse event or suspected adverse reaction is considered "serious" (**Serious Adverse Event or SAE**) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- **Death:** Report if you suspect that the death was an outcome of the adverse event and include the date if known.
- **Life-threatening:** Report if suspected that the patient was at substantial risk of dying at the time of the adverse event or use or continued use of the device or other medical product might have resulted in the death of the patient.
- **Hospitalization (initial or prolonged):** Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.
 - Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- **Disability or Permanent Damage:** Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
 - **Congenital Anomaly/Birth Defect:** Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- **Required Intervention to Prevent Permanent Impairment or Damage (Devices):** Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
- **Other Serious (Important Medical Events):** Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may

jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Study personnel are expected to adhere to the [Einstein OHRA Other Reportable Events Policy](#) and [Unanticipated Problems Policy](#) for these matters. Personnel utilizing the BRANY IRB should review the [Information Sheet for Researchers Unanticipated Problems Involving Risks to Participants or Others](#).

Research Billing Compliance

All clinical research activity conducted at Montefiore Medical Center and its affiliates must be compliant with the [Research Billing Compliance Policy](#) to ensure that research and standard of care procedures are distinguishable and billed for accordingly.

Research Funds and Financial Management

Payments received for Investigator Initiated clinical research activities are managed by the Office of Clinical Trials. The OCT oversees the accounting and reconciliation of payments with clinical trial activities via their CTMS records, to ensure trials are funded in alignment with the clinical trial agreement. The Biomedical Research Alliance of New York (BRANY) manages the finances of industry sponsored clinical trials activity.

Principal Investigators at Montefiore Medical Center receiving payments from a sponsor have research fund accounts established and managed by the [Office of Research Sponsored Programs \(ORSP\)](#), or the [Office of Grant Support](#) if the research grant is being awarded to Albert Einstein College of Medicine.

Investigators should contact their department (research) administrators in order to open a research fund account. Payments received from BRANY for Industry Sponsored Clinical Trials are also managed by ORSP or the Office of Grant Support.

STUDY CLOSE-OUT

The study close-out process consists of several steps intended to ensure that a study can be archived according the GCP standards once the activities and terms agreed to in the Clinical Research Agreement have been executed. A sponsor can initiate study close-out for the following reasons:

- The study protocol has been executed and completed
- The sponsor has terminated the study prematurely due to circumstances including but not limited to poor recruitment, lack of funding, protocol deviations, inadequate documentation or ethical concerns.

Close Out Visit

Study sponsors may conduct a *Close-Out Visit* in order to bring the study to a proper close at the local site. Here, the sponsor's aim is to clarify any open questions about the data collected,

to ensure that any investigational medicinal products, medical devices and study materials remaining are dealt with correctly, and to discuss responsibilities after the end of the study. A study cannot be officially closed out until all queries are addressed, data is analyzed, publications are submitted, documentation is stored, and the study is closed with the IRB.

The Office of Clinical Trials conducts a Financial Close-Out at the end of a trial for all studies managed by the OCT. During this time, OCT conducts a thorough review of the Clinical Research Agreement to ensure that all monies due to the investigator, institutions, and any other relevant parties have been collected and reconciled. To learn more about OCT's financial close-out process, please contact the [Office of Clinical Trials](#).

Investigators should ensure the following items are completed prior to Sponsor's Close-Out Visit:

- All study visits must be completed by all subjects at the local site.
- All Case Report Forms (CRFs) and source documents are completed
- The Investigator and Coordinator complete all requests for data corrections or verifications on CRFs and return them to the Sponsor.
- Any and All test articles are collected from all Subjects. All used and unused test articles are inventoried, any discrepancies in the test article log are noted.
- Test article supplies are returned to the Sponsor in the manner specified. All containers are returned to the Sponsor.
- Copies of the test article logs, final inventory, and return documents are filed in the regulatory documentation binder.
- All Sponsor-required reports are completed. A copy is filed in the regulatory binder and a copy sent to the Sponsor.
- Complete final report for Institutional Review Board (IRB), notifying them that the study is closed. A copy of the report is sent to the Sponsor and filed in the regulatory documentation binder.
- Coordinator reviews the regulatory documentation binder and recovers any missing documents. If documents cannot be found, the Sponsor is notified and a waiver is placed in the regulatory documentation binder.
- Coordinator arranges for secure storage of the CRFs, source documents, and regulatory documentation binder, and informs the Sponsor of the storage location.

IRB Close-Out Notification

Once notice from the sponsor regarding study closure has been received, Investigators must notify the appropriate local IRB of study closure.

Document Storage

After a study is closed, and all study documents are reviewed and completed, the regulatory binders and other study documents can be archived in accordance with institutional policies. It will be stored in a safe place and made available in the event of a Sponsor or FDA and/or other applicable regulatory authority audit.

Good Clinical Practice (GCP) requires certain essential documents to be kept by the PI for the conduct of a clinical trial at three specific time points (for investigational drug and device trials):

1. Before the clinical phase of the trial commences
2. During the clinical conduct of the trial
3. After completion or termination of the trial.

Document Storage for Sponsor-Investigators

There are added responsibilities regarding the essential documents when the PI also is the sponsor of the study. While the PI is ultimately responsible for the implementation and conduct of the research at a given site, as the sponsor, the PI is also responsible for protocol development, quality control, study management, data and record keeping. For complete requirements, please review the [ICH's Guidance for Industry E6 GCP: Consolidated Guidance](#).

Archiving

The archiving process involves storing research study documents off site. Copies of all case report forms are retained by the Investigator, in accordance with federal regulations ([Code of Federal Regulations 21 CFR 312.68](#)). CRFs should be retained for study subjects, including those who died during a clinical study or those who did not complete the study as a result of an adverse event.

It is recommended that investigators ensure archiving costs are included in the research budget. For assistance negotiating these costs into your clinical study budget, contact the [Office of Clinical Trials](#) or the [Biomedical Research Alliance of New York](#). Investigators who are ready to archive their study records should follow their departmental Standard Operating Procedures and contact their respective departmental Research Administrator for guidance.

NOTE: Investigators must be aware that when a decision is made to dispose of research records, the disposal must be done in a manner to protect confidentiality. The Investigator should obtain written notification from the sponsor prior to any record destruction.

How Long to Archive?

- [NIH policy](#) requires holding records related to research supported in whole or in part by NIH grants or contracts for a minimum of three years after the submission of the final fiscal report for the funding instrument.
- [The FDA](#) requires that data obtained in an FDA regulated studies (studies conducted under an IND or IDE) be retained until two years after marketing approval or after the withdrawal of the IND
- The contract with the sponsor generally outlines the exact requirements for archiving study documents.
- Adhere to [Einstein Office of Human Research Affairs Record Retention Policy](#).

Typical procedure for storing research documents and records

- Contact your Departmental Research Administrator for guidance
- All research records submitted for offsite storage must be in standard storage boxes. Each box will be given an individual barcode label which is affixed to the front of the box. An inventory sheet will be completed for each box submitted.
- A specific disposal date should be indicated on the box
- Ensure an archive tracking system is in place. The following information should be retained on the tracker:
 - Trial/Protocol number
 - IRB number
 - PI-name and contact
 - Date archived
 - Total number of boxes
 - Destruction date
- Principal Investigators should notify the sponsor/CRO that the study data is being removed from the site and stored in an off-site facility.

For more information on document storage, please see the Einstein OHRA Policy on [Required Documentation for the Conduct of Research Involving Human Subjects](#).

APPENDIX – STUDY TEMPLATES & CHECKLISTS

Delegation of Responsibility Log

Principal Investigator: _____

Protocol Title: _____

IRB #: _____

RESPONSIBILITY	PERSONNEL	DATE
Study Administration		
Protocol feasibility		
Study Budget		
Budget Negotiations		
Contract Negotiations		
Fiscal Management		
Protocol Management		
Database Management		
Risk Management		
Quality Assurance/Control		
Protocol Activities		
Sponsor/CRO Contact		
IRB Submission/Communication		
Regulatory Files		
Patient Recruitment		
CRF Completion		
Reporting Adverse Events		
Source Documents/Tools		
Protocol Training		
Test Article Accountability		
Study Supplies Accountability		
Monitor Visits		
Subject Management		
Eligibility Screening		
Informed Consent/Assent		
Subject Scheduling		
Subject Education		
Subject Visits		
Medical Exams		
Clinical Assessments		
Adverse Event Determination		
Source Documentation		
Study Closeout		
Final Document Storage		
Final Report		
Publication		

The individuals listed above are qualified and trained to carry out the responsibilities I have delegated to them. I assert that these duties will be performed under my direct supervision.

Principal Investigator Signature

Date

Enrollment Log

PRINCIPAL INVESTIGATOR: _____ **STUDY TITLE:** _____

PROTOCOL #: _____ **SPONSOR:** _____

ICF signed? Y N	Version	Subject Name	Date	Subject No.	Contact Information or MRN

Drug Accountability Log

Study Title:

PI:

Coordinator:

Drug Name:

**Dose Form and
Strength:**

**Drug Storage
Location:**

Shipment		Subject Identifier	Subject Initials	Lot Number	Expiration Date	Dispensing			Balance Forward	Comments
Date	Quantity					Date	Quantity	Dispensed By		

Principal Investigator Signature: _____

Date: _____

Ongoing Essential Regulatory Document Checklist

Protocol Title:

Protocol Number:

IRB Number:

Document Name	Version # and/or Date	Located In Regulatory Binder?	Sent to Sponsor?	If Deficient, Corrective Action Taken and Date	Auditor's Initials
Current Version of Protocol on file					
Protocol Amendments with signed Signature Page					
Original 1572 (signed)					
Updated 1572 (signed)					
Signed Financial Disclosures for all listed on 1572-give date in next column					
Current CVs w/ Cover Letters & Current License For all listed on 1572-list date in next column					
Current IRB Roster					
Current Laboratory Certifications-local and central					
Current Laboratory Normal Values-local and central					
IND (If applicable)					
Investigator's Brochure and Revisions					
Signature Sheet with all listed on 1572 (Site Signature Log)					
Miscellaneous					

Auditor's Signature: _____

Date: _____

Essential Document Binder Checklist

A completed Regulatory Binder/Essential Document Binder should contain the following documents. Investigators should use this checklist as a guideline for ensuring organization and GCP compliance with study document maintenance. This checklist can be placed at the beginning of the regulatory binder(s). Depending on the nature of a trial or protocol, some of the following items may not apply:

- Study contact sheet
- Final Protocol
- Protocol Signature Pages
- Amendments to protocol
- Amendment Signature Page
- Investigator's Brochure/Device Manual/ Package Insert
- Amendments to Investigator Brochure
- Signed FDA 1572
- All amended FDA 1572
- Device agreement (device studies)
- Investigators' Curricula Vitae (CVs), CITI Certification, Licenses
- CV's of clinical research staff
- Financial disclosure documentation
- Delegation of Responsibility/ Signature Log
- Study Personnel Education/Training
- Screening/Enrollment Log
- IRB Federal Wide Assurance Letter
- IRB approval letters for original protocol, advertisement and recruitment material and informed consent form and HIPAA authorization forms
- IRB approved translated consent
- IRB approval for all amendments
- Original signed consent form(s) for each subject (can be maintained in the subject binder)
- Subject Consent Log
- Internal and external communications relating to the study: letters, memos
- Monitoring visit log and any reports or correspondence
- Laboratory certification, lab normal reference ranges for each lab used
- CV and credentials of lab director
- Drug accountability log and shipping records
- Decoding procedures
- Information relating to the test article
- At the end of the study copy of the test article randomization code

- Temperature charts for drug storage
- Adverse event information occurring at the site including IRB submission notifications of SAE's
- Copies of all CRF's and any other data forms including lab test data
- Final study report to IRB
- Other – Blank Case Report Forms (CRFs), Data Collection Sheets, Standard Operating Procedures (SOPs), Procedure Manuals, IND Reports, Notes to File

Deviation Log

IRB #:		PI Name:					
Subject ID#	Date of Deviation	Description of Deviation	Reportable to Sponsor (Y/N)	Date Sent to Sponsor	Reportable to IRB (Y/N)	Date Sent to IRB	PI Initials and date
		Corrective Action:					
		Corrective Action:					
		Corrective Action:					
		Corrective Action:					
		Corrective Action:					

Adverse Event Log

IRB #:				PI Name:								
Subject ID#	Date of Onset	Date Resolved	Outcome*	Seriousness**	Relationship***	Unanticipated (Y/N)	Action with Study Treatment****	Reportable to Sponsor (Y/N)	Date Sent to Sponsor	Reportable to IRB (Y/N)	Date Sent to IRB	PI Initials and date
Event Description:												
Event Description:												
Event Description:												
Event Description:												
Event Description:												

***Outcome**

1. Resolved
2. Resolved with sequelae
3. Recovering
4. Not Recovered/Not Resolved
5. Fatal
6. Unknown

****Seriousness**

1. Fatal
2. Life-threatening
3. Serious
4. Not Serious

*****Relationship**

1. Definite
2. Possible
3. Probable
4. Unlikely

******Action with Study Treatment**

1. No Action
2. Interrupted
3. Discontinued

Study Close-Out Checklist

Protocol _____

Sponsor _____

Primary Investigator _____

Date _____

- Study documents file is complete
- Study Closure/ Final Report has been made to IRB
- Copy of IRB Study Closure/ Final Report to sponsor
- Confidential patient list on file at _____ address, if applicable
- All Case Report Forms (CRFs) or EMR are completed and submitted to sponsor
- All CRF/EMR corrections/queries have been addressed
- All source documentation is in order and included with CRFs
- If not with study files, location of materials or additional materials is noted here _____
- Study personnel form is complete
- Subjects' signed informed consents are filed
- Drug dispensing logs and disposition forms are complete, if applicable
- Study drug has been returned per sponsor instructions
- All other study materials (extra CRFs, etc.) have been returned or destroyed
 - Note specifics _____
- Investigator Brochure and IND safety reports are filed
- All study materials are filed together as per archival procedures
- Sponsor notified of record storage location
- Additional notes _____
- Form completed by _____

Tissue Log

PRINCIPAL INVESTIGATOR: PROTOCOL #: SUBJECT #:					STUDY TITLE: SPONSOR: DRUG:			
			Informed Consent			Sharing and Transferring Repository Samples		
	Subject Code (Study ID)	Date Sample was Obtained	Date of Consent	Consent Options	Copy of Signed and Dated Consent Given to Subject	Collaborators	Mode	Date Sent to Collaborator
				<i>Refer to option key</i>		<i>Refer to collaborator key</i>	<i>Refer to mode key</i>	
1.					<input type="checkbox"/>			
2.					<input type="checkbox"/>			
3.					<input type="checkbox"/>			
4.					<input type="checkbox"/>			
5.					<input type="checkbox"/>			
6.					<input type="checkbox"/>			
7.					<input type="checkbox"/>			
8.					<input type="checkbox"/>			
9.					<input type="checkbox"/>			
10.					<input type="checkbox"/>			
11.					<input type="checkbox"/>			
12.					<input type="checkbox"/>			
13.					<input type="checkbox"/>			
14.					<input type="checkbox"/>			
15.					<input type="checkbox"/>			
16.					<input type="checkbox"/>			
17.					<input type="checkbox"/>			
18.					<input type="checkbox"/>			

Training Documentation Log

PRINCIPAL INVESTIGATOR: PROTOCOL #: SUBJECT #:	STUDY TITLE: SPONSOR: DRUG:
---	--

TRAINING CONDUCTED BY: PRINCIPAL INVESTIGATOR:		SIGNATURE OF PERSON CONDUCTING THE TRAINING: SIGNATURE OF PRINCIPAL INVESTIGATOR:¹	Date: Date:
---	--	--	--------------------

Description of Training (attach hand-outs, if applicable):

NAMES OF STAFF WHO RECEIVED TRAINING	TITLE AND ROLE ON PROJECT	STAFF SIGNATURES ¹	Date

¹ Your signature indicates that you have reviewed the indicated SOPs or attended the training described and have had your questions answered

Essential Documents: Before the Clinical Phase of the Trial Commences

Before the Clinical Phase of the Trial Commences	
During this planning stage the following documents should be generated and should be on file before the trial formally starts	
DOCUMENT	PURPOSE
INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator
SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF
IRB APPROVED INFORMED CONSENT FORM (ICF) (including all applicable translations)	To document the informed consent
ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent
ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive
FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial; Investigators may insert a note to file in this section, stating that financial documents are securely stored with the Office of Clinical Trials
INSURANCE STATEMENT	To document that compensation to subject(s) for trial-related injury will be available; Investigators may insert a note to file in this section, stating that financial documents are securely stored with the Office of Clinical Trials
SIGNED AGREEMENT BETWEEN INVOLVED PARTIES	To document agreements; Investigators may insert a note to file in this section, stating that financial documents are securely stored with the Office of Clinical Trials

<p>DATED, DOCUMENTED IRB APPROVAL OF THE FOLLOWING:</p> <ul style="list-style-type: none"> • CRF (if applicable) • Informed Consent Form(s) • Any other written information to be provided to the subject(s) • Advertisement for subject recruitment (if used) • Subject compensation (if any) • Any other documents given approval 	<p>To document that the trial has been subject to IRB review and given approval; To identify the version number and date of the document(s)</p>
<p>FEDERAL REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)</p>	<p>To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)</p>
<p>CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)</p>	<p>To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects</p>
<p>NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL</p>	<p>To document normal values and/or ranges of the tests</p>
<p>MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS</p> <ul style="list-style-type: none"> • certification or • accreditation or • established quality control and/or external quality assessment or • other validation (where required) 	<p>To document competence of facility to perform required test(s) , and support reliability of results</p>

<p>INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)</p>	<p>To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials</p>
<p>SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</p>	<p>To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability</p>
<p>DECODING PROCEDURES FOR BLINDED TRIALS</p>	<p>To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment</p>
<p>TRIAL INITIATION MONITORING REPORT</p>	<p>To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)</p>

Essential Documents: During the Clinical Conduct of the Trial

During the Clinical Conduct of the Trial	
In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.	
DOCUMENT	PURPOSE
INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available
<p style="text-align: center;">ANY REVISION TO:</p> <ul style="list-style-type: none"> • protocol/amendment(s) and CRF • informed consent form • any other written information provided to subjects • advertisement for subject recruitment (if used) 	To document revisions of these trial related documents that take effect during trial
<p style="text-align: center;">DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</p> <ul style="list-style-type: none"> • protocol amendment(s) • revision(s) of: <ul style="list-style-type: none"> ○ informed consent form ○ any other written information to be provided to the subject ○ advertisement for subject recruitment (if used) ○ any other documents given approval • continuing review of trial (where required) 	To document that the amendment(s) and/or revision(s) have been subject to IRB review and were given approval/favorable opinion. To identify the version number and date of the document(s).
REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:	To document compliance with applicable regulatory requirements

CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects
UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial
UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS	To document that tests remain adequate throughout the trial period
DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability
SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission
SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject
SIGNED, DATED AND COMPLETED CRFs	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded
DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded
NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11
NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2

NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2
INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3
SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening
SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject
SUBJECT ENROLMENT LOG	To document chronological enrolment of subjects by trial number
INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol
SIGNATURE SHEET	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs
RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated

Essential Documents: After Completion or Termination of the Trial

After the Completion or Termination of Trial	
After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following	
DOCUMENT	PURPOSE
INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor
DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site
COMPLETED SUBJECT IDENTIFICATION CODE LIST	To document destruction of unused investigational products by sponsor or at site
FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial
CLINICAL STUDY REPORT (If applicable)	To document results and interpretation of trial

Investigational Site Inspection Checklist

The following items may be addressed during an Investigational Site Inspection:

- Staff General Interview
 - Study personnel involved (investigator, study coordinator, etc.)
 - Knowledge of protocol and procedures
- Process of protocol implementation
- Investigator obligations
- Review participant enrollment
- Method of participant recruitment
- Participant eligibility
- Informed consent procedures
- Participant enrollment log
- Participant enrollment violations
- Review Protocol and Regulatory Compliance
- Site specific IRB requirements
- Congruence of appointment schedule with participant's visits recorded on CRFs
- Participant follow-up procedures
- Protocol violations and deviations
- Review Essential Document File
 - *Signed Investigator Agreement*
 - *Curriculum(a) Vitae for investigator (s)*
 - *Signed protocol and any amendments*
 - *Instructions for Use*
 - *IRB address and, if requested, membership list (or Assurance Number)*
 - *IRB Reports/Approvals:*
 - *Initial approval of protocol, any amendments, and informed consent*
 - *Annual renewal approval (if > 1 year study)*
 - *Interim reports (if required by IRB)*
 - *Final report*
 - *IRB correspondence*
 - *General correspondence*
 - *Laboratory certificate of accreditation*
 - *Laboratory reference ranges for all protocol required tests*
 - *Authorized study personnel signature sheet*
- Review Consent Forms
 - *Contains all required elements*
 - *Signed and dated form for each subject on file*
 - *Ensure most current version was used*
 - *Ensure consent was signed before the first protocol-required procedure*
 - *Check for documentation of the consent process in the source documents*
- Review Case Report Forms (CRFs)
 - *Verify method of CRF completion*
 - *Verify congruence of CRF with source documents*

- *Training for eCRF*
- Review Source Documents
 - *Assure appropriate documentation of premature study termination (if applicable)*
 - *Verify records retention policy*
 - *Review Investigational Product Dispensation*
 - *Investigational product storage and security*
 - *Product shipping orders*
 - *Returned supply inventory forms*
 - *Confirm adequacy of investigational product accountability records*
- Check Equipment and Facilities
 - *Verify test/exam room adequacy*
 - *Assure documentation of lab certification*
 - *Assure documentation of instrument calibration/maintenance*
- Review Adverse Experience (AE) Reports
 - *Confirm AE reporting system*
 - *Review all serious AE's*
- Review Participant Records
- Check Monitoring Log
- Conduct exit interview with investigator and staff
- Address questions and concerns

Common Deficiencies Noted in Inspections Study Conduct

- Failure to protect the rights and welfare of subjects
- Failure to obtain subject consent
- Inappropriate payment to volunteers
- Use of investigational product before IDE approval
- Failure to report AEs
- Failure to obtain IRB approval
- Failure to communicate with IRB on changes and absence of progress reports
- Inappropriate delegation of Investigator's authority
- Failure to list additional investigators
- Integrity and Validity of Data
 - *Submission of false information*
 - *Problems with records availability*
 - *Inadequate and inaccurate records*
 - *Inadequate adherence to protocol*
 - *Unapproved concomitant therapy*
 - *Simultaneous use of multiple investigational products*

Be prepared to discuss the following in detail:

- The consent process
- The process for recruiting subjects

- Delegation of responsibility by the PI
- The CRF/EDC completion process
- SAE reporting process
- How the PI maintains his/her oversight of the project
- Concurrent trials
- If an extension trial is being audited have information on the parent trial available
- Frequency of monitoring visits and how long monitor stayed at site during visit
- Study drug:
 - *Study drug randomization and kit assignments.*
 - *If automated randomization process used, ensure all fax confirmation and other documents are available*
 - *Drug accountability and reconciliation*
 - *Storage area is locked and temperature is monitored*
 - *Ensure study drug not dispensed is being kept separate from study drug that has been returned/dispensed*
 - *Ensure there is written documentation for the process of transporting study drug from one center to another*
 - *If drug is kept on site ensure documentation for a waiver has been approved*

Exit Interview

- The FDA may issue the following-
 - *Form FDA 483 (Notice of Observations) used for violations of the Federal Regulations*
 - *Establishment Inspection Report*
- Appoint a person to document the exit interview between the PI, member of the IRB and Auditor
- Document each observation provided on the Form FDA 483 and be sure they are understood
- Point out any deficiency noted in the observation that has been corrected since the beginning of the audit (it might be removed). If it is not removed have the auditor indicate that it has been corrected on the form
- If any observation noted deals with FDA regulations, carefully point out that the regulations are subject to interpretations and if correct that “our interpretation was intended to provide the greatest protection to our patients”.
- If corrective action on an observation is indicated and that it will be taken, indicate that the appropriate corrective action will be taken immediately.
- If you believe an observation is not warranted, you should point it out
- Be sure you clearly understand the observations
- Once the exit interview is over the inspector will submit a written report to headquarters. The letter is generally one of three types:
 - *Notice of no significant deviations from regulations were observed*
 - *Informational letter-identifies deviations from GCP and may or may not require a response from the PI*

- *Warning Letter-identified deviations that need prompt correction by the PI. The Sponsor and IRB may be notified. The FDA may take other courses of action including regulatory, legal or administrative sanctions.*
- A corrective or preventative action plan, if indicated should be submitted to the IRB in advance of submission to the Regulatory Agency.
- All correspondence received from regulatory agencies before, during and after the inspection should be submitted to the IRB.

Common FDA Findings

- Protocol
 - *Are all versions in the Investigator File*
 - *Are all protocol signature pages signed for all versions of the protocol*
- Investigator Brochure (IB)
 - *Are all versions in the Investigator File*
 - *Are all signature pages signed for all versions*
 - *If all versions are not in the Investigator File is there a memo stating where older versions of IB can be found?*
- Form FDA 1572
 - *Is it correctly signed and dated? Is there more than 1 form, is the most current form filed with the IRB and Sponsor? Has section #8 been appropriately completed?*
- CV
 - *Does the site have CV's for everyone listed on the 1572; are they signed and dated within the last 2 years?*
 - *Does the CV document the PI's affiliation with the site?*
 - *Are current medical licenses and CITI certificates filed?*
- Confidentiality Agreement
 - *Was it signed before the release of any study documents?*
- ICF
 - *Copy of IRB approved consents on file?*
 - *Changes to consent on file?*
 - *All IRB approval letters on file*
 - *Have the patients been participating in the trial under the correct version of the consent?*
 - *Are all versions of the consent signed and dated properly?*
 - *If translated consents are used has a certified translator documented the translation? Is there a copy of the back translation?*
 - *If study has enrolled minors, have the guardians signed the consent, is an approved assent being used?*
 - *Have all consents been signed prior to any study related procedures being performed?*
- Serious Adverse Events
 - *Have all SAE's been reported to the CRO, sponsor, IRB*
 - *Within the proper time frame?*

- *Has the SAE been followed to resolution?*
- *In the event the patient died is there a copy of the death certificate in the source documents?*
- Institutional Review Board
 - *Documentation of the IRB membership list*
 - *Can all IRB approvals be easily tracked?*
 - *Are periodic reviews appropriately submitted to the IRB? Is the IRB response filed in the investigator binder?*
 - *Are study summaries sent to the IRB upon study completion?*
 - *Are SAE's being appropriately reported?*
 - *Are protocol deviations being reported?*
 - *Does the IRB respond to these reports? Is the documentation filed in the investigator binder?*
- Site Visit Follow Up Documentation
 - *Are issues identified during a site-monitoring visit followed up in subsequent visits? Is there documentation to indicate that these issues have been resolved?*
- Laboratory Documentation
 - *Are appropriate lab certificates filed for local lab and/or central lab – CLIA, CAP*
 - *Normal lab values on file*
- Investigator Supplies
 - *Can all supplies be accounted for*
 - *Are the supplies being stored properly*
 - *Are temperatures being monitored*
- Site Equipment
 - *Has equipment been serviced recently, are logs available*
 - *If calibration is required, has it been performed prior to study initiation, is there documentation?*
- Correspondence
 - *Is there sufficient correspondence between site and sponsor, CRO, IRB to demonstrate ongoing communications for the duration of the study*
- Research Charts
 - *Does the subject's chart capture sufficient information to demonstrate participation in a trial?*
 - *Does the information transcribed on the CRF substantiate the research chart?*
 - *Are AE's and SAE's recorded in the chart?*

For additional information, refer to Einstein OHRA [Audit and Inspection Guidelines](#) and [Audit Policy](#):

Protocol Elements Checklist

(From the Einstein OHRA)

Use this checklist as a guide to ensure that a protocol to be submitted for IRB review is scientifically sound and adequately designed, and that you have included all the required elements. This outline includes statistical recommendations that have been provided by the Division of Biostatistics. Some of these may not be applicable to a feasibility study or a pilot study in which the analyses are mainly descriptive. It is highly recommended that you consult with a statistician prior to submission of a protocol for review.

1) Background/Significance

- a) Include an evaluative review of the state of current knowledge in the area of the research and indicate how the study builds on or extends this body of information.
- b) The review should clearly place the research in context to form the basis for its rationale.
- c) Present the results of any pilot studies.

2) Study Design

- a) Describe the study design, e.g. clinical trial (phase I, II, III); observational cohort study; case-control study.
 - State study objectives, and if applicable, specific hypotheses
 - Clearly state target population and recruitment methods
 - State inclusion/exclusion criteria clearly
 - State primary and secondary outcome(s)
 - For Randomized clinical trials
 - Indicate whether a parallel or crossover study, and the number of treatment groups
 - Describe randomization and blinding procedures
 - Describe what safety outcomes will be monitored
 - Include a data safety monitoring plan
 - For Observational studies
 - Describe predictors of interest along with potential confounders and effect modifiers
 - Describe matching criteria, if applicable
 - Describe duration of follow-up, and timing of data collection
- b) Describe the planned interventions and their timing.
- c) Define the outcome measures pertaining to each aim.

3) Study Population

- a) Describe the study population: number, age range; health status or other characteristics pertinent to the study

- Describe how the sample size and power of the study were determined, including the statistical approach and any assumptions on which the calculations are based.
- Take into account anticipated drop-out or loss-to-follow up rate.
- Pilot and exploratory studies do not need formal sample size calculations but a data analysis plan should still be included (see above)

b) State inclusion/exclusion criteria.

c) Provide appropriate justification for the exclusion of any population group (e.g. Minors, Women, Ethnic groups, Non-English Speaking people, etc.)

[N.B. federal regulations require inclusion of women, minors and minority group members in research unless adequate justification is provided. Acceptable justifications for exclusion of minors are listed below in Appendix 1].

d) State whether subjects who do not have the capacity to consent will be enrolled.

- Provide justification for inclusion of such subjects.
- Describe how surrogate consent will be obtained.

e) Identify the sources of research material.

- State whether materials will be obtained from individually identifiable living human subjects.
- Indicate the type of material (e.g. blood samples, tissue specimens, records, data, etc.)
- Indicate whether the material will be obtained as part of routine clinical care or for the specific purpose of research.

4) Participant Recruitment

a) Describe the plan for participant recruitment.

b) Describe sources and method(s) for recruitment of both subjects and controls.

c) Describe the method(s) for ensuring voluntariness of participation.

d) Describe the plan for Patient Privacy protection.

5) Informed Consent

a) Provide an Informed Consent Form containing all of the necessary elements (see below).

b) Describe the informed consent process.

- Who will obtain consent?
- Where will consent be obtained?

c) Provide clear justification if a waiver or alteration of the informed consent process is requested.

d) If minors are included, describe the plan for parental approval and child assent.

- e) Describe any costs or remuneration:
 - State any reimbursement or remuneration, including the pro-rating scale if multiple visits are required.
 - Clearly identify tests and procedures as for Research Purposes or Standard Clinical Care.
 - Include a listing of any costs (tests/procedures/supplies which are the responsibility of the subject).
- f) For studies with complicated schedules, provide a 1-page table or flow diagram.
- g) Stat the plan for obtaining HIPAA authorization (or waiver as appropriate).

6) Risk/Benefit

- a) Identify all anticipated risks (e.g. medical, social, psychological, and/or legal).
- b) Describe how anticipated risks will be minimized.
- c) Document how potential benefits to participants or others justify potential risks.
- d) Describe the plan for data storage and for maintenance of subjects' confidentiality.
- e) If subjects will be video or audio-taped, address the following: What will be taped, how the tapes will be used, when the tapes will be destroyed, and whether taped subjects will be compensated.

7) Data Analysis

- a) Clearly state statistical methods to be used to evaluate study objectives
- b) Describe methods for interim analyses or early stopping, if applicable
- c) Describe how possible confounding and/or effect modification will be addressed
- d) Describe how loss to follow up will be addressed

8) Data quality control and database management.

- a) Describe methods for data entry and data management.
- b) Describe the mechanism for checking and editing the data.
- c) Describe computer data security and subject confidentiality. This is particularly important for multicenter studies.

References: Include a bibliography of all references in the protocol

Appendix 1: Criteria for Exclusion of Minors from Research protocols

1. the research topic to be studied is irrelevant to children;
2. there are laws or regulations barring the inclusion of children in the research. For example, the regulations for protection of human subjects allow consenting adults to accept a higher level of risk than is permitted for children;
3. the knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. NIH

program staff can be contacted for guidance on this issue if the information is not readily available;

4. a separate, age-specific study in children is warranted and preferable (consult NIH Policy for specific example of such studies).
5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). While children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
6. Study designs aimed at collecting additional data on pre-enrolled adult study participants (e.g., longitudinal follow-up studies that did not include data on children).
7. Other special cases justified by the investigator and found acceptable to the review group and the Institute Director.