**Standard Operating Procedures for Conducting Clinical Research**

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# About This Manual

## Scope

This Manual sets forth the institutional oversight and basic policies and operational procedures for the Conduct Clinical Trials and its “Partner/Investigative Sites”. This manual is not an operating manual for an Institutional Review Board, Institutional Bio-safety Committee or any committee or function that oversees Conduct Clinical Trials assistance with external researchers for their research protocols. The purpose of these policies and procedures is to ensure that when Conduct Clinical Trials is responsible for the actual research component of research activity (not simply the billing or IRB oversight) that such research is conducted in accordance with applicable regulations, including those issued by the federal agencies with oversight of human subject research. Research activity will also be subject to applicable state laws and regulations that may be more restrictive than federal regulations.

# Definitions and Acronyms

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | 510(k) | A particular FDA Class For Medical Devices | | |  |
|  | AE | Adverse Event | | |  |
|  | CFR | Code of Federal Regulations | | |  |
|  | CMS | United States Center for Medicare and Medicaid Services | | |  |
|  | CCRA | Certified Clinical Research Associate | | |  |
|  | CCRC | Certified Clinical Research Coordinator | | |  |
|  | CPI | Certified Physician Investigator | | |  |
|  | CRA | Clinical Research Associate | | |  |
|  | CRC | Clinical Research Coordinator | | |  |
|  | CRF | Case Report Form | | |  |
|  | CRO | Contract Research Organization | | |  |
|  | DHHS | United States Department of Health and Human Services | | |  |
|  | DOT | United States Department of Transportation | | |  |
|  | DSMB | Data Safety Monitoring Board | | |  |
|  | FDA | United States Food and Drug Administration | | |  |
|  | FWA | Federal-Wide Assurance | | |  |
|  | GCP | International Council on Harmonization’s *E6: Good Clinical Practices* | | |  |
|  | HIPAA | Health Insurance Portability and Accountability Act of 1996 | | |  |
|  | HUD | Humanitarian Use Device (FDA Class of Medical Devices) | | |  |
|  | IATA | International Air Transport Association | | |  |
|  | IB | Investigator’s Brochure | | |  |
|  | ICH | International Council on Harmonization | | |  |
|  | IDE | Investigational Device Exemption (FDA Class For Medical Devices) | | |  |
|  | IDMC | Independent Data Monitoring Committee | | |  |
|  | IND | Investigational New Drug (FDA Class For Drugs) | | |  |
|  | IRB | Institutional Review Board | | |  |
|  | IVRS | Interactive Voice Response System | | |  |
|  | NDA | New Drug Application (FDA Class For Drugs) | | |  |
|  | NIH | United States National Institutes of Health | | |  |
|  | NSR | Non-Significant Risk (FDA Risk Classification of Medical Device) | | |  |
|  | PHI | Protected Health Information as defined by the Health Insurance Portability and Accountability Act of 1996 | | |  |
|  | PMA | Pre-Market Application (FDA Class For Medical Devices) | | |  |
|  | PI | Principal Investigator | | |  |
|  | SAE | Serious Adverse Event | | |  |
|  | SMO | Site Management Organization | | |  |
|  | SOP | Standard Operating Procedures | | |  |
|  | SPOOS | Significant Payments Of Other Sorts | | |  |
|  | SR | Significant Risk (FDA Risk Classification of Medical Device) | | |  |
|  | UAE | Unexpected Adverse Event | | |  |
| Term | | | Definition | Additional Sources | |
| Adverse Event (AE) | | | Any untoward medical occurrence in a patient or clinical investigation subject administered a product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. | ICH GCP 1.2 | |
| Assent | | | A child’s affirmative agreement to participate in a clinical investigation. Mere failure to object may not, absent affirmative agreement, be construed as assent. | 21CFR50.3(n)  45CFR46.402(b) | |
| Case Report Form (CRF) | | | A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each trial subject. | ICH GCP 1.11 | |
| Children | | | Persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted. | 21CFR50.3(o)  45CFR46.402(a) | |
| Clinical Research Coordinator (CRC) | | | The person at the site who manages the daily operations of a protocol and who is responsible to the Principal Investigator. |  | |
| Contract Research Organization (CRO) | | | A person or organization that assumes, as an independent contractor with the Sponsor, one or more of the obligations of a Sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration. | ICH GCP 1.20 | |
| Clinical investigation | | | Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. | 21CFR50.3(c)  21CFR56.102(c) | |
| Data and Safety Monitoring Board (DSMB) | | | A committee of scientists, physicians, statisticians and others that collects and analyzes data during the course of a research study to monitor for adverse effects (events) and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the study involves a placebo control) that would warrant modification or termination of the study or notification of subjects about new information that might affect their willingness to continue in the study. Also called Data Monitoring Committee. | ICH GCP 1.25 | |
| Delegated Authority | | | The power given to an individual by the Principal Investigator as evidenced only in writing on the Delegation of Authority Log (or equivalent) and housed in the Regulatory Binder. |  | |
| Double-Blind | | | The design of a study in which neither the investigator nor the subject knows which treatment the subject is receiving. |  | |
| Expedited review | | | Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the convened IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research. |  | |
| Family Member | | | Any one of the following legally competent persons: Spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship. | 21CFR50.3(m) | |
| Guardian | | | An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. | 21CFR50.3(s)  45CFR46.402(d) | |
| Human Subject | | | An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. Alternatively, a living individual about whom an investigator (whether professional or student) conducting research obtains;  (1) Data through intervention or interaction with the individual, or (2) Identifiable private information. | 21CFR50.3(g)  21CFR56.102(e)  21CFR312.3(b)  21CFR812.3(p)  45CFR46.102(f)  ICH GCP 1.57 | |
| Inclusion/Exclusion Criteria | | | The characteristics that must be present (inclusion) or absent (exclusion) in order for a subject to qualify for a research protocol. |  | |
| Independent Data Monitoring Committee (IDMC) | | | See Data Safety and Monitoring Committee. |  | |
| Institutional Review Board (IRB) | | | Any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. | 21CFR50.3(i)  21CFR56.102(g)  21CFR812.3(f) | |
| Investigational New Drug (or Investigational Drug) (IND) | | | An investigational drug is a drug or biologic that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The FDA considers the term “Investigational New Drug” synonymous. | 21CFR312.3(b) | |
| Investigational device | | | A device, including a transitional device that is the object of an investigation. | 21CFR812.3(g) | |
| Investigational Product | | | An Investigational Drug or Device. |  | |
| Investigator | | | An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. In the event that an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. | 21CFR50.3(d)  21CFR56.102(h)  21CFR312.3(b)  21CFR312.3(i)  ICH GCP 1.34 | |
| Investigator's Brochure (IB) | | | A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. | ICH GCP 1.36 | |
| Interactive Voice Response System (IVRS) | | | A telephone contact system that allows the user to key in requests and receive instructions or information. |  | |
| Legally Authorized Representative | | | An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in the research. | 21CFR50.3(l)  45CFR46.102(c)  ICH GCP 1.36 | |
| Medical Monitor | | | The physician at the Sponsor who is responsible for the clinical investigation of a test product. |  | |
| MedWatch | | | The FDA Medical Products Reporting Program is an initiative designed to educate health professionals about the critical importance of monitoring for and reporting adverse events and problems to FDA and/or the manufacturer and to ensure that new safety information is rapidly communicated to the medical community, thereby improving patient care. The purpose of the MedWatch program is to enhance the effectiveness of post-marketing surveillance of medical products as they are used in clinical practice and to rapidly identify significant health hazards associated with these products. |  | |
| Minimal Risk | | | The degree of risk in which the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. | 21CFR50.3(k)  21CFR56.102(i)  45CFR46.102(i) | |
| Monitor | | | When used as a noun, means an individual designated by a Sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a Sponsor or a consultant to the Sponsor, or an employee of or consultant to a contract research organization. Monitor, when used as a verb, means to oversee an investigation, specifically the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s). | 21CFR812.3(j)  ICH GCP 1.38 | |
| Open-Label | | | A study in which the subjects and the investigator are aware of the treatment the subject is receiving (i.e. not single-blinded or double-blinded). |  | |
| Parent | | | A child’s biological or adoptive parent. | 21CFR50.3(p)  45CFR46.402(c) | |
| Placebo | | | An inactive substance designed to resemble the article being tested. |  | |
| Principal Investigator | | | See Investigator. |  | |
| Protocol | | | A plan that includes, at minimum, the objectives, rationale, design, methods and other conditions for conducting a research study.  Alternatively, a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. | ICH GCP 1.44 | |
| Randomization | | | The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. | ICH GCP 1.48 | |
| Research | | | A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. | 45CFR46.102(d) | |
| Research Coordinator | | | See Clinical Research Coordinator. |  | |
| Research Staff | | | Staff directly involved in research related activities. This is meant to include roles such as Principal Investigator, Sub-Investigator and Clinical Research Coordinator. Although other staff may interact with research subjects, for purposes of this manual the term “Research Staff” does not include support staff such as billing, dietary etc. |  | |
| Serious Adverse Event (SAE) | | | Any untoward medical occurrence that:   1. Results in death, 2. Is life-threatening (places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death) 3. Requires inpatient hospitalization or prolongation of existing hospitalization, 4. Results in persistent or significant disability/incapacity, or 5. Is a congenital anomaly/birth defect.   Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (21CFR312.32(a)) | ICH GCP 1.50 | |
| Significant Payments Of Other Sorts (SPOOS) | | | Payments made by the Sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a monetary value of more than $25,000, excluding the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study. | 21CFR54.2(f) | |
| Source Documents | | | Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial). | ICH GCP 1.52 | |
| Sponsor | | | An entity (person or organization) who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a Sponsor (not a Sponsor-investigator), and the employees are considered to be investigators. | 21CFR50.3(e)  21CFR56.102(j)  21CFR312.3(b)  21CFR812.3(n)  ICH GCP 1.53 | |
| Sponsor-Investigator | | | An individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency. | 21CFR50.3(f)  21CFR56.102(k)  21CFR812.3(o)  ICH GCP 1.54 | |
| Sub-Investigator | | | Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial related procedures and/or to make important trial-related decisions (e.g., associates, residents, or research fellows). | 21CFR312.3(b)  ICH GCP 1.56 | |
| Subject | | | See Human Subject |  | |
| Test Article | | | Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the FDA or other federal regulations. | 21CFR50.3(j)  21CFR56.102(l) | |
| Trial Site | | | The local institution where the research activity will actually be conducted. | ICH GCP 1.59 | |
| Unexpected Adverse Event (UAE) | | | Any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. (21CFR312.32(a)) |  | |
| Vulnerable Subjects | | | Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. | ICH GCP 1.61 | |
| Ward | | | A child who is placed in the legal custody of the State or other agency, institution, or entity, consistent with applicable Federal, State, or local law. | 21CFR50.3(q) | |
| Well-Being | | | The physical and mental integrity of the subjects participating in a research protocol. | ICH GCP 1.62 | |

# Administrative Policies

### Overview, Regulatory Support and References:

Policy manuals are made to reflect what we do, and what we do should be reflected in policy manuals. Policies provide the framework for consistent behavior, as well as a uniform and quite often evidence-based methodology for dealing with situations. Policy manuals are a resource that allows employees to get on with their jobs and not have to keep on discussing and re-discussing the same issues every time they arise (i.e. thought out decisions can be applied to many similar cases with efficiency).

Regulations and their standards of conduct concerning research change over time; therefore, policies should either lead or immediately follow these trends. Not only must policies be continuously reviewed and timely updated as necessary, people must also be familiar with them and able to comply with them as they are revised.

Ideally, all policies are followed and there is a policy for everything we do. The real world, however, demonstrates that policies are deviated from either intentionally or unintentionally. This may result from a simple misinterpretation of the policy, lack of knowledge of the policy, disregard of the policy or the simple inability of a manual to address every potential situation. Lack of knowledge should be avoided by education. Unintentional deviations should be avoided by training. Intentional deviations should be necessary and, unless enacted to prevent harm to subjects, pre-approved. Repeated requests for deviations should prompt a revisiting of the policy to assure it is meeting the needs of research operations.

## Policies on Standard Operating Procedures (“SOPs”) for Research

Policy Number: SOPR-ADMIN-100.V01

#### Effective Date: July 10, 2016

**PURPOSE:** To provide a policy manual to be used as a training tool, a methodology to assure compliance with regulations, a methodology to strategically decrease variance between providers as necessary and receive all the other benefits that a policy manual provides.

**POLICIES:**

1. Conduct Clinical Trials has a Standard Operating Procedures (SOP) manual in place, which governs the conduct of clinical research (including clinical trials) at partner sites.
2. Periodic, but no less than every two years, review of these policies shall be performed.
3. Ad-hoc reviews of a specific policy should be done in the presence of the following:
   1. Passing of a new law or regulation affecting that policy to assure compliance.
   2. Issuing of a new guidance document pertaining to that policy to determine if the guidance is to be adopted.
4. Whenever a new policy, a revision to an existing policy or the deletion of a policy is needed, appropriate review of said policy is completed. A historic record is kept so that on any given date, it can be easily determined what policy was in place.
5. From time to time, deviations from this policy will either occur or be necessary in “single case” scenarios. If prior written approval for such deviation from the Institutional Official is not possible (i.e. emergent need or discovered negligence that occurred in the past), the Institutional Official is to be informed as soon as possible after the deviation occurs.

### Procedure for Periodic Review of SOPs

1. The relevant governing body(ies) of Conduct Clinical Trials shall review the most current version of this manual in its entirety, at least every two years and, provided no changes are necessary, adopt the Manual and its subsequent revisions until the next review.
2. Changes in regulations or guidance should prompt a review of the relevant policies in this manual.

### Procedure for Additions/Modifications/Deletions To SOPs

1. Unless initiated by the Institution‘s Official, in the event that a particular policy is requested to be generated or modified or deleted, a written request to the Institutional Official containing the following information will be sent prior to implementing the change. Such request should address the following information:
   1. The relevant policy number (for modification or deletion requests); AND
   2. The reason for requesting the addition/modification/deletion
      1. Statements such as “required by law/accrediting body/etc.” cannot be considered unless accompanied by the relevant citation or copy of such external requirement; AND
   3. The proposed change (preferably in a redline format) or new policy that molds to the same format as this manual; AND
   4. Any other relevant information.
2. Once received, the Institutional Official will research the policy request and decide the following:
   1. Compliance with relevant federal, state and local laws as well as GCPs
   2. Approval “As-Is”; Approval with modifications (and provide modifications); OR Disapproval (with justifications)
   3. Such decisions should be done in conjunction with, or at minimum reported to, a corporate responsible executive for clinical research for purposes of guidance or that it may pertain to other Sites within the scope of their service. As appropriate, the Institutional Official or a corporate responsible executive for clinical research may initiate the modification.
3. To maintain historic integrity on NEW policies…
   1. A Version tag (i.e. “.V01”) or version date shall be placed in the policy number.
   2. An Effective Date shall be provided in the policy header
4. To maintain historic integrity on MODIFIED policies…
   1. The Version tag shall be increased to reflect the next version (e.g. .V01 to .V02)
   2. An Effective Date shall be provided in the policy header
   3. The old policy shall be kept in an Archive section of the manual for a period pertaining to the record retention section in this manual.
5. To maintain historic integrity on DELETED policies…
   1. A Version tag of “.V-DELETED” shall be placed as the policy number.
   2. The Title of the Policy shall be changed to include the words “DELETED POLICY” prior to the rest of the title.
   3. The archived policy shall note the date as no longer effective.
   4. As necessary, a description of the reason for deletion.
   5. The deleted policy shall be kept in an Archive section of the manual for a period pertaining to the record retention section in this manual.

### Procedure for Planned and Temporary SOP Deviation

1. When circumstances arise requiring activity inconsistent with the SOPs, permission should be obtained prior to the activity whenever possible. The criteria for a planned SOP deviation is as follows:
   1. The change is necessary to protect the safety of staff/subjects AND/OR the protocol calls for procedures contrary to our SOPs; AND
   2. The change is temporary, individual to a certain situation and not sufficient to request a permanent change to the policies.
2. The request for temporary policy deviation is to be sent to the Institutional Official in writing with the following information:
   1. Policy Number/Section necessary to deviate from
   2. Justification for deviation
3. Once received, the Institutional Official will research said policy deviation request and decide the following:
   1. Compliance with relevant federal, state and local laws as well as GCPs
   2. Compliance with any corporate compliance policies (directly or indirectly governing research) may require review by a corporate responsible executive for clinical research.
   3. Approval “As-Is”; Approval with modifications (and provide modifications); OR Disapproval (with justifications)
   4. If approved, documentation of the Institutional Official approval shall be kept in the research files for the protocol.

## Training on, Availability of, and Interpretation of SOPs

Policy Number: SOPR-ADMIN-110.V01

Effective Date: July 10, 2016

**PURPOSE:** Without the relevant staff being knowledgeable of the policies, the best-written policies are useless.

**POLICIES:**

1. All staff members are to be trained on the most recent version of this manual prior to undertaking their duties.
2. Changes to SOPs are to be communicated to relevant staff with sufficient time prior to their effective date to accomplish the transition to the new procedures.
3. The manual shall be readily available to those that will need it for reminders.
4. The Institutional Official shall be the ultimate authority on the interpretation of and resolution of any ambiguity in this manual.

### Procedure for Initial SOP Training and Routine Review

1. At a minimum, the following staff shall receive access to a complete copy of this manual prior to undertaking duties:
   1. Principal Investigators that are either
      1. Employed OR
      2. Otherwise engaged on behalf of the Site
   2. Sub-Investigators that are either
      1. Employed OR
      2. Otherwise engaged on behalf of the Site
   3. Clinical Research Coordinators that are either
      1. Employed OR
      2. Otherwise engaged on behalf of the Site
2. As research involves ancillary staff at the Site (e.g. billing, business development etc.), these staff should be aware of at least the relevant portions pertaining to their duties.
3. At initial employment/engagement, the entire manual must be reviewed via a customary training/education methodology.

### Procedure for Manual Availability

1. At all times, a copy of this manual must be available at the Site for staff to review in paper or electronic form. This can be accomplished in one of many ways such as:
   1. Print Version.
2. Research Staff should be readily able to state where this manual is located.
3. Unless absolutely necessary, multiple paper copies of policies should be discouraged to prevent version control issues and loss of confidentiality of business practices.

### Procedure for Interpretations of SOPs

1. Questions concerning any ambiguities or uncertainties in this manual are to be routed to the Institution Official.
2. The policies shall be interpreted locally by the Institutional Official in accordance to the stipulation of the law, guidance and the company’s mission statement.
3. Any disagreements with the Institution Official’s interpretations are encouraged to be voiced, particularly if there is an ethical or legal concern. This may lead to the written clarification of the policy or bring into light additional information that may influence a change in the interpretation.
4. A corporate, responsible executive for clinical research shall have the final authority on such interpretations.
5. Any employee has a right to follow the usual compliance policies (i.e. on reporting compliance issues) in the event they believe that an interpretation is unethical or illegal.

# Informed Consent

### Overview, Regulatory Support and References:

Informed consent is a hallmark ethical requirement regarding research with human subjects. Informed consent is not simply a form or a one-time event, but an ongoing process that begins before the subject is enrolled and lasts until after they have completed participation in the research project. Informed consent is the combination of the state of understanding the nature of the research activity and the ability to voluntarily choose whether or not to begin or continue participation. Adherence to ethical principles as well as federal/local laws not only protects both the subject’s autonomy and the investigator from liability, but also fosters public trust in the research process to which medical progress is dependent.

* 21 CFR50.23, 24, 25(a)(1-8), 25(b)(1–6), 27(b)(2)
* 45 CFR46.116(a)(1-8), 116(b)(1–6), 117(a), 117(b)(2), 117(c)
* ICH Harmonized Tripartite Guideline E6: Good Clinical Practice: 1.9, 4.8.1, 4.8.3, 4.8.5, 4.8.7, 4.8.8, 4.8.9, 4.8.10, 4.8.11, 4.8.15 (<http://www.fda.gov/cder/guidance/959fnl.pdf>)
* FDA Information Sheets—The Consent Process (<http://www.fda.gov/oc/ohrt/irbs/informedconsent.html>)
* OHRP: Tips On Informed Consent (Revised 3/16/93) <http://www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm>
* OHRP: Obtaining And Documenting Informed Consent Of Subjects Who Do Not Speak English (November 9, 1995) <http://www.hhs.gov/ohrp/humansubjects/guidance/ic-non-e.htm>
* OHRP: Informed Consent--Legally Effective and Prospectively Obtained (August 12, 1993) <http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc93-03.htm>

1. OHRP: "Exculpatory Language" in Informed Consent (November 15, 1996) <http://www.hhs.gov/ohrp/humansubjects/guidance/exculp.htm>

* IRB Guidebook III A and B (<http://www.hhs.gov/ohrp/irb/irb_chapter3.htm#e2>)

## Policies on Informed Consent Content

Policy Number: SOPR-IC-100.V1

Effective Date: July 10, 2016

**PURPOSE:** Information presented to potential and active subjects should be of sufficient detail for them to adequately make an informed decision about initial or continued participation.

**POLICIES:**

1. Required Elements of Consent
   1. Informed consent (whether written, verbal or both) must have all the required elements unless the IRB has waived the requirement for that element of consent.
   2. The Required Elements of consent are consistent with law (both federal and state) as well as the ICH Good Clinical Practices as applicable. For example:
      1. A statement that the study involves research;
      2. An explanation of the purposes of the research;
      3. The expected duration of the subject’s participation;
      4. A description of the procedures to be followed;
      5. Identification of any procedures which are experimental, including a description of administration of any study drugs;
      6. As appropriate, the probability for random assignment to each of the protocol’s arms (i.e. research group, placebo group, control group etc.);
      7. A description of any reasonably foreseeable risks or discomforts to the subject;
      8. A description of any benefits to the subject or to others which may reasonably be expected from the research;
         1. When there is no intended clinical benefit to the subject (i.e. the benefit is solely limited to a sense of helping the public at large), the subject should be made aware of this.
         2. Payments or other remuneration to the subject are not considered to be expected benefits.
      9. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
      10. A description of the extent, if any, which confidentiality of study data identifying the subject will be maintained (NOTE: The Health Insurance Portability and Accountability Act of 1996 (HIPAA)) has certain written language required to disclose information for research purposes. This language may be utilized in a separate “Stand-Alone” form or in combination with other research consents as allowed by law. In the event that a separate form is not used, the elements required by that form are to be included in this informed consent document- See section on Privacy in this manual for more information);
          1. If the investigational product is governed by the FDA, then this section must note the possibility that the Food & Drug Administration may also inspect the records;
      11. For research involving more than minimal risk (which includes non-physical risks such as social or financial risk), an explanation as to whether any compensation is available if injury occurs and, if so, what it consists of, who will be responsible for paying, and where further information may be obtained;
      12. For research involving more than minimal risk (which includes the danger of non-physical risks such as psychological risks), an explanation as to whether any medical treatment is available if injury occurs and, if so, what it consist of, who will be responsible for paying, and where further information may be obtained;
      13. An explanation of i) whom to contact for answers to pertinent questions about the research; ii) whom to contact for questions concerning research subjects’ rights; and iii) whom to contact in the event of a research-related injury to the subject;
          1. All three areas must be addressed in the document
          2. One person/agency cannot be the contact for all three areas. There must be at least two separate entities addressing these three items (e.g. Principal Investigator or Study Coordinator as the person(s) to contact for questions about the study and about injuries; and the IRB as the entity to contact for questions about rights) with local telephone numbers for contacts to answer questions in these areas.
          3. If any of the numbers are long distance numbers, a Toll Free or Collect-Call option should be given
      14. A statement that participation is voluntary
      15. A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled (NOTE: use of that exact phrase is preferred as opposed to “not affect your treatment at this Facility” or other phrase that may imply other limitations)
      16. A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled (NOTE: use of that exact phrase is preferred as opposed to “not affect your treatment at this Facility” or other phrase that may imply other limitations).
      17. For applicable clinical trials (consult FDA guidance for definition of applicable clinical trials), the **exact** following statement *“A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”*
2. Additional Elements of Consent Forms
   1. Similar to the above Required Elements of Consent, informed consent (whether written, verbal or both) must include the following additional elements consistent with law (both federal and state) as well as the ICH Good Clinical Practices as applicable unless the IRB has waived the additional requirement.
   2. Additional elements include:
      1. ELEMENT: A statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, which are currently unforeseeable- CRITERIA: Any study that involves currently unforeseeable risks to the subject or to an embryo or fetus, if the subject is or may become pregnant (this is especially true with studies conducted under an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE));
      2. ELEMENT: Anticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent- CRITERIA: Any study in which the protocol outlines circumstances under which the subject’s participation may be terminated without regard to the subject’s consent (Note: an unexplained statement that the investigator and/or the Sponsor may withdraw subjects at any time does not adequately inform the subject of anticipated circumstances for such withdrawal);
      3. ELEMENT: Any additional costs to the subject that may result from participation in the research- CRITERIA: Any study in which the subjects may incur additional costs because they are participating in research (i.e. co-payments, deductibles or denial of coverage on some insurance and/or other reimbursement mechanisms may not fund some or all procedures that are delivered in a research context);
      4. ELEMENT: The consequences of a subject’s decision to withdraw from the research and procedures for orderly termination of participation by the subject- CRITERIA: Any protocol in which withdrawal may have deleterious effects on the subject’s health or welfare or would result in additional procedures (example: continuous hospitalization to restabalize on a different medication);
      5. ELEMENT: A statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject- CRITERIA: Any study in which the subject’s participation is expected to continue over a period of time during which new findings may become available to investigators or the public;
      6. ELEMENT: The approximate number of subjects to be involved in the study- CRITERIA: The IRB determines that the number of subjects in a study is material to the subject’s decision to participate (this is particularly true in studies involving small numbers of subjects, as in Phase 1 and 2 studies);
      7. ELEMENT: BOTH the amount AND schedule of any remuneration to subjects for their participation- CRITERIA: Studies involving remuneration to subjects.
3. Understandability: The information that is given to the subject or the representative shall be in a language that is understandable to the subject or the representative.
   1. The consent process (particularly any written documents) should be conducted in the subject’s native language,
   2. The consent process (particularly any written documents) should be at a level understandable by the prospective subjects (NOTE: “Level understandable” does not necessarily equate to grade level as determined by scales like the Flesch-Kincaid. Although these scales may be used as an aid, they should not be a stand-alone determination of understandability as they do not evaluate the content of the language such as sequencing, cadence, validity etc.). This is a subjective interpretation of the IRB taking all things into consideration.
4. Non-exculpatory Language Requirement: No informed consent may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the their legal rights, or releases or appears to release the investigator, the Sponsor, the institution or its agents from liability for negligence.
   1. In written consent forms, although not required, language such as the following is suggested:
      1. Avoidance of phrases such as “I understand…”
      2. Avoidance of certifying language such as “This study has been fully explained to me”
      3. Avoidance of overly optimistic or reassuring language such as “This study has been approved by an ethics board that has already determined that the potential benefits outweigh the risks” or “This drug is in the final stages of approval”.
      4. Use of Second-Person Writing style is recommended so the form reads as if “I/we” are the investigators and “you” is the subject.
5. The IRB has the ultimate authority on interpretation of what is allowable or not allowable in the informed consent documents. Any decision on the IRB’s part that is contrary to the spirit of human subject protection should be brought to the attention of the Institution Official.
6. Ideally all required information should be presented at one time (e.g. in a single document) to prevent confusion or accidental omission of a required element. If a staging technique is a necessary part of the study, the initial presentation should explain that subjects will be asked to participate in the additional phases. It should be clear whether the phases are steps in one study or separate but interrelated studies.
7. All elements of consent that the IRB requires should be in writing and signed by the subject (or their legal representative) unless otherwise waived by the IRB.
8. Any Informed Consent Document, Waiver of Documentation of Informed Consent, Waiver of Informed Consent or Waiver/Alteration of Required Elements of Informed Consent etc. must have prior approval by the IRB.

## Policies on Obtaining Informed Consent

Policy Number: SOPR-IC-110.V1

#### Effective Date: July 10, 2016

**PURPOSE**: Information presented to potential and active subjects should be understandable and non-coercive for them to adequately make an informed decision about initial and/or continued participation. Documentation of the process should be of sufficient detail so that the state of informed consent can be easily ascertained.

**POLICIES:**

1. Only the Principal Investigator or his/her delegate for this purpose may initiate the informed consent process.
2. The initial informed consent process takes place before any investigational product is administered, or the administration of any control articles or research-related interactions or interventions that otherwise would not be performed, absent the research. For example, if an individual is admitted to the hospital and would receive a History and Physical Examination but not an ECG as part of that admission- if the protocol requires both for screening, the informed consent may be completed before or after the History & Physical Exam but the ECG may only be done after the subject has consented (in writing unless documentation of consent has been waived by the IRB, then verbally) to be in the study. This policy item may be amended if the federal criteria and necessary approvals for Emergency Research or other waivers of consent are met and obtained respectively.
3. The initial informed consent process shall ideally take place at one of the locations where the research will take place. This will give the subject a chance to be better informed about the research environment. Exceptions may be made at the subject’s request or other reasonable circumstances.
4. Potential subjects (or their legal representative) should be offered the opportunity to participate in a study only under circumstances that provide sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.
   1. The information that is given to the subject or the representative shall be in a language that is understandable to the subject or the representative.
   2. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the Sponsor, the institution or its agents from liability for negligence.
5. The subject or their representative shall have adequate space, time and privacy to read any and all documents pertaining to initial informed consent before anything is signed. The subject or their representative shall be allowed to take the Informed Consent home and discuss with primary care physician or family members, if the Informed Consent is not being signed under urgent care needs.
6. Conduct Clinical Trials shall allow for the governing IRB or their representative to fulfill their legal responsibility to observe the informed consent process at any time pursuant to their review should they deem it necessary.
7. A Subject shall not be allowed to sign an Informed Consent Form until all of his/her questions have been answered to their understanding.
8. The subject should have the option to have the Informed Consent Form read to them if they so choose.
9. A subject should not be allowed to sign the Informed Consent if a member of the Primary Investigator or his/her delegate does not feel as if the subject understands the requirements of the Informed Consent or if they feel as if the subject is under any influence that could be impairing the subjects decision-making process.

### Procedure for Delegating Informed Consent

1. Any delegate authorized by the Principal Investigator to conduct the informed consent process should be:
   1. Adequately trained as defined in the training policy.
   2. Documented (e.g. listed on a Delegation of Authority form) in the Regulatory Binder or other study files.
   3. Listed as a sub-investigator on the FDA Form 1572, if applicable.
2. Additions of delegates should have start dates.
3. Deletions of delegates should have end dates.

### Procedure for Consenting Non-English Speaking Subjects

1. Studies should be described to subjects in their native language.
2. Whenever it is planned to enroll non-English speaking individuals, a translated consent document should be approved by the IRB in advance.
   1. The translation should be performed by a company with core competencies in this area and not an ad-hoc/informal translation.
3. In the event of an unexpected encounter of a non-English speaking subject, an oral translated presentation may be done accompanied with the procedure for a “Short Form” that is in the native language of the subject.
   1. Additional documentation on how the subject understood the information presented is required. Similar to documenting the understanding of English speaking individuals, a simple note of “the subject understood the information presented” does not describe in sufficient detail how this understanding was evidenced.

### Procedure for Consenting Illiterate Subjects

1. CRITERIA: A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if:
   1. The person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) AND;
   2. Is able to indicate approval or disapproval to study entry, they may be entered into the study.
2. A note to file should document the method used for communication with the prospective subject (i.e. oral presentation).
3. An impartial third party should witness the entire consent process and sign the consent document as a witness.
4. For those who cannot write, a signature can be accomplished by "making their mark" on the consent document, when consistent with applicable state law.

### Procedure for Assent of Children

1. Conduct Clinical Trials, in conjunction and compliance with the IRB for a given study, must determine whether the subject does or does not have capacity to consent for themselves under local law. This may include review of information such as:
   1. Age
   2. Emancipation/Marital Status
   3. Other legal documents
2. The parent/guardian is the entity who gives “consent” and the child is the entity that provides “assent”. Note that assent is not an absence of evidence of disagreement. Assent requires an active sign of agreement by the child.
3. Based on the degree of risk and benefits of the study, the IRB determines if it is only necessary for one parent/guardian to sign the consent form when there are two or more parents/guardians. In general, even if only one signature is required by law or by IRB, it is preferred that all parental parties concur with the child’s participation whenever possible.
   1. When the IRB requires two signatures, the second signature may only be waived when one parent is deceased, unknown, incompetent or when the child is in the sole legal custody of one parent. The one parent must provide justifying evidence and copies of such should be placed in the research records in order to proceed.
   2. When the child is a ward of the state or other custodial institution, the proper state signatory for medical purposes is considered the official signatory however the child must be appointed an advocate independent of both the custodial institution and MD Trials. The advocate need not co-sign nor be present for the consent process but needs to be aware of the consent. An individual can be an advocate for more than one ward. Note that any remuneration awarded by the study goes to the custodial agency and not to the signing official personally.
4. Based on the nature of the study, the IRB shall determine if assent may be waived.
5. Proper clinical judgment should be used if here is need to inform the child and parents separately to prevent coercion.
6. Although a special form is not required by this policy (only documentation in the study notes), a Sponsor or IRB may request the child sign an Assent Form.
   1. This form does not have to duplicate all the required elements of an informed consent document but must give sufficient explanation of the study in an age-appropriate manner.
   2. This form should be at an education level equivalent to or below that of the child’s. Several Assent Forms may be used for the same study enrolling varying age groups, any/all of which must have prior approval by the IRB in a manner similar to an informed consent document.
   3. The same methodology on items such as distribution of copies, version controls etc. as used for consent forms should be used for Assent Forms.
7. Regardless of whether an assent form is used or not, a detailed progress note should be documented indicating how the child understood what was explained verbally and/or in the consent document. A statement that “the subject understood the information presented” is not adequate, as it does not explain how this was determined. Recall that assent is not an absence of evidence of disagreement. Assent requires an active sign of agreement by the child and this sign should be documented.

### Procedure for Obtaining Revised Informed Consent

1. The Principal Investigator, IRB or Sponsor may initiate a proposed change of the content of an Informed Consent Document; however, the IRB has the final authority over the document.
   1. All changes to consent forms should strive to be a “stand alone” document. It should not be a simple paragraph describing the changes unless necessary and approved.
   2. Note, if documentation of consent has been waived by the IRB, any changes to required elements of consent shall still be given verbally and a written account shall be documented of this process.
2. No subjects should be presented with a revised consent document until it has been approved by the IRB; however, disclosing information relevant to their participation (i.e. a newly discovered unexpected, serious and related adverse event) should not be withheld verbally because the form had not been finalized and a written account shall be documented of this process.
3. The site shall ensure that there is a system that identifies the most currently approved consent document that eliminates the potential use of older versions (i.e. a date stamp or version number).
4. Copy of IRB approval shall be kept in the study files (e.g. in the Regulatory Binder). Whenever practical, a “track-changes” or “red-lined” version should be filed to easily compare the old version with the new version.
5. The following classes of subjects shall be asked to sign the revised IRB approved form.
   1. New subjects to the study
   2. Current subjects to which the changes apply
      1. Example: If the study adds an ECG on visit 2; all subjects past that visit need not sign the revised consent form unless the ECG was added because a previously disclosed cardiovascular risk was identified.
   3. Any other class as instructed by the IRB.
6. The timing of re-consent shall be appropriate to the degree of risk of the change. For example, re-consenting people in a drug study due to a new discovery of increased chance of kidney failure should be done promptly as opposed to re-consenting subjects due to the protocol of adding a Quality of Life questionnaire.

### Procedure for Documenting Informed Consent

1. Unless consent or documentation of consent has been waived by the IRB or the Short Form is used, there should be an informed consent form signed AND dated by:
   1. The subject (or their legal representative)
   2. The person conducting the consent discussion
   3. A witness or PI signature (unless the PI is the person conducting the consent discussion) is not required by this policy but supported if required by the IRB or Sponsor. Note that a witness signature is needed for use of the Short Form as discussed in that policy.
2. An original signed consent document shall be kept in the research files. IN ADDITION, it is also required to have:
   1. One copy given to the subject
3. All Informed Consent Discussions shall be documented on the Informed Consent Discussion Form (see attachment A) and a brief note that this was completed shall be added to the screening visit notes and any other visits that re-consent are applicable.
   1. For subjects which may have compromised decision-making abilities due to their illness (e.g. psychiatry studies), documentation of their mental status as it pertains to decision-making at the time of consent.
4. For ongoing consent, each visit should ensure that the subject is still informed and willing to continue with the study. It should be documented in the visit progress notes that this process of ongoing consent was asked prior to any study procedures.
   1. Verbal acknowledgement of understanding a newly developed risk(s). You will need to document the discussion with the subject, in detail.
   2. For subjects which may have compromised decision-making abilities due to their illness (e.g. psychiatry studies), documentation is done of their mental status as it pertains to decision-making at the time of consent.

# Institutional Review Boards (IRB)

### Overview, Regulatory Support and References:

The Principal Investigator is ultimately responsible for all study activity, including data integrity, operations, recruitment, scheduling and many other things including, ultimately, the protection of the rights and well-being of the research subjects. The IRB is an administrative body with autonomy independent of the Principal Investigator that aids the investigator by providing exclusive, objective and representative focus in the area of protection of the rights and well-being of human subjects. The membership represents the community and statutorily includes, among other things, both scientific and non-scientific members. Although no committee can ever be a substitute for a concerned Principal Investigator exercising integrity in his/her decisions, a properly run IRB offers an objective, multidiscipline, publicly-oriented and (most importantly) binding concern to all aspects of the research that pertain to the protection of human subjects.

* 21CFR56.107; 56.114; 312.64; 312.66
* 45CFR46.107(a); 46.114
* FDA Information Sheet (1998): Non-Local IRB Review (<http://www.fda.gov/oc/ohrt/irbs/nonlocalreview.html>)
* FDA Information Sheet (1998): Cooperative Research (<http://www.fda.gov/oc/ohrt/irbs/research.html>)
* FDA Information Sheet (1998): Sponsor-Investigator-IRB Relationship (<http://www.fda.gov/oc/ohrt/irbs/toc4.html>)
* OHRP Guidance (7/9/1991) “General Guidance On The Use Of Another Institution's IRB” (<http://www.hhs.gov/ohrp/humansubjects/guidance/irb-rely.htm>)
* OHRP Memorandum (2/4/97) “Update - Suitability of a Designated Institutional Review Board (IRB)” (<http://www.hhs.gov/ohrp/humansubjects/guidance/ind-irb.htm>)
* OHRP Memorandum (1/26/99) “Engagement of Institutions in Research” (<http://hhs.gov/ohrp/humansubjects/assurance/engage.htm>

## Communications with the IRB

Policy Number: SOPR-IRB-120.V01

##### **Effective Date: July 10 2016**

**PURPOSE:** The IRB must be fully informed of the human subject research activity to best fulfill their role in human subject protection. Conduct Clinical Trials/Principal Investigator must be fully informed of the IRB’s decisions to aid in his/her/their protection in human subjects as well.

**POLICIES:**

1. No non-exempt study involving human subjects may begin without having the written approval from the IRB in hand. Verbal approval is not acceptable.
2. All information included below, if applicable, and any additional information deemed necessary by the IRB should be submitted timely.
3. Investigative Site shall maintain all correspondence to and from the IRB in the research files (e.g. in the Regulatory Binder) or other appropriate area in the study files for the study.

**Procedures for Submitting for Initial Review**

1. Investigative Site will submit all requested information to the IRB, typically needing the following:
   1. Proposed research plan (or request exemption from IRB review) including any of the below that is relevant or requested:
      1. Protocol
      2. Informed Consent Form (or request for waiver of consent or waiver of documentation of consent)
      3. Information on the Informed Consent Process including as required by the IRB
         1. Who will conduct the informed-consent process
         2. When the process will take place
         3. Where the process will take place
         4. How the investigator will determine that the subject or representative understands what has been explained
         5. What opportunity will be afforded to the prospective subject, or the legally authorized representative, to consider whether or not to participate
         6. For studies that will continue over a period of time, how the investigator will determine the ongoing consent of the subject
      4. Proposed Advertisements
      5. Identification of Risks that may result from the research
      6. Sources of those risks
      7. How risks have been minimized
      8. Impact of various components on study design as it pertains to its increasing and decreasing risks
      9. How safety will be monitored (DSMB or otherwise)
      10. Sponsor’s classification of any medical devices (NSR or SR status), if applicable
      11. If Vulnerable Subjects are included,
          1. Justification for their inclusion in research
          2. Additional safeguards to protect the rights and welfare of the vulnerable subjects
      12. The probable benefits to the research subjects or a statement indicating that there are no probable benefits to the subject.
      13. The importance of knowledge reasonably expected from the research
      14. Methods to obtain information about participants
      15. Provisions for protecting the confidentiality of research data
      16. List of qualified clinician(s) (investigator or sub-investigator) responsible for all study-related healthcare decisions
      17. Attestation that the investigator will refer subjects for needed health care during research or for follow-up after the research
2. If the Sponsor submits any of this on the Investigator’s behalf, documentation of such should be maintained and investigative site should be kept apprised of any discussions.
3. All correspondence to and from the IRB should be filed in the study files (e.g. the Regulatory Binder) or other designated location.

**Procedures for Submitting New Information, Continuing Reviews and Termination Reports**

1. As the study progresses, the Principal Investigator shall submit the following to the IRB according to IRB policy:
   1. Proposed changes in research, including but not limited to;
      1. Proposed changes in the protocol
      2. Proposed changes in consent forms
      3. Other proposed changes made to improve the protection of subjects
   2. Reports on deviations from the approved protocol or other regulations and policies
   3. Reports on unanticipated problems (including adverse events)
   4. Reports on unanticipated problems involving risks to subjects
   5. Continuing review data, including;
      1. Number of subjects entered in the study
      2. Gender of subjects entered into the study
      3. Minority status of subjects entered into the study
      4. Any other information specified by the IRB
   6. Any other information affecting human subject protection.
   7. Study termination/completion reports
2. This information must be submitted in the shorter of the timeframes dictated by the IRB, protocol, this policy or law.
3. File all correspondence to and from the IRB in the study files (e.g. in the Regulatory Binder).
4. Continuing Review shall be submitted within the sooner of the IRB’s deadline or one year from the previous approval date. It is the PI’s responsibility to assure timely submission regardless of any courtesy reminders given or errors made by the IRB.
5. If the Sponsor submits any of this on the Investigator’s behalf, documentation of such should be maintained and kept appraised of any discussions.
6. Continuing review should be submitted with sufficient lead time (preferred at least one month) to allow for any mishaps in processing and to avoid any unnecessary suspension in research activity due to lapsed approval.

# Audits/Inspections

### Overview, Regulatory Support and References:

To substantiate the integrity of trial data collected. To substantiate that the Primary Investigator of the study has followed the protocol as approved by the regulatory authorities and as stated in the investigator Agreement in the 1572 (See attachment 1572).

* ICH GCP Consolidated Guideline – 4.9.7
* FDA 1572

# Policies on Audits and Inspections

Policy Number: SOPR-AAI -100.V1

Effective Date: July 10, 2016

**PURPOSE:** To substantiate the integrity of trial data collected. To substantiate that the Primary Investigator of the study has followed the protocol as approved by the regulatory authorities and as stated in the Investigator Agreement in the 1572 (See attachment 1572).

**POLICIES:**

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

**Primary Investigator Responsibilities**:

Primary Investigator (PI) agrees to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes to a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. PI agrees to personally conduct or supervise the described investigation(s). PI agrees to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and PI will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. PI agrees to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. PI agrees to read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug. PI agrees to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments. PI agrees to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68. PI will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, PI will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. PI agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

## IRB Audits

Policy Number: SOPR-IRB-130.V01

##### **Effective Date: PROPOSED July 10, 2016**

**PURPOSE:** To aid the IRB’s process in their dedicated function of protecting human subjects.

**POLICY:**

1. Investigative Site shall make reasonable accommodations for the IRB to audit the operations or consent process.

# Monitoring Visits

### Overview, Regulatory Support and References:

Monitoring visits are typically conducted at clinical sites to determine compliance with federal regulations, adherence to GCP/ ICH guidelines, to verify the validity and integrity of clinical data collected by the research coordinator in source documentation and transcribed to case report forms, to assure that confidentiality of the protocol as well as subject data is being maintained, and that the facilities and staffing are adequate for continued participation in the study.

* Title 21 CFR 52.47 Proposed Obligations of Sponsors and Monitors
* Title 21 CFR 54.15 Proposed Obligations of Clinical Investigators
* Guidelines for Monitoring of Clinical Investigations, 1988
* ICH GCP Consolidated Guideline Part 4 Investigator
* ICH GCP Consolidated Guideline Part 5.18 Monitoring

## Policies on Interim Monitoring Visits

Policy Number: SOPR-IMV-100.V1

Effective Date: July 10, 2016

**PURPOSE:** To outline activities required for facilitating and monitoring visits during the course of a clinical investigation.

**POLICIES:**

Monitoring visits will occur within normal business hours and are scheduled ahead of time with the research coordinators.

The Clinical Research Associate (CRA), affiliated with either the pharmaceutical company or Contract Research Organization (CRO), contacts the research coordinator to schedule a visit.

1. Once the visit is scheduled, the research coordinator will contact everyone involved in the visit. This includes: Investigational Drug Services, Principle Investigator, Compliance or Unit Manager.
2. The study coordinator will gather all study-related records including CRFs, source documents and regulatory files for subjects who consented for the protocol. They will contact Medical Records for all original clinic or hospital chart(s) for any episode of care for all CRFs associated with the trial. Off-site medical records and missing records will be requested in an attempt to obtain them prior to the visit.
3. The principal investigator will be available during the monitored visit for any questions or clarification that needs to be made. If the scheduled date of the audit is inconvenient for the principal investigator, the study coordinator may contact the CRA to request rescheduling at a mutually convenient time.
4. The regulatory compliance or unit manager will meet with the CRA at the conclusion of the visit to discuss any questions or findings.

# Investigator Record Keeping and Record Retention

### Overview, Regulatory Support and References:

Record keeping and Record Retention are to be conducted and managed in accordance with the following regulations:

* Title 21 CFR 312.62
* ICH GCP Consolidated Guideline – 4.9.5
* ICH GCP Consolidated Guideline-Part 8

# Policies on Investigator Record Keeping and Record Retention

Policy Number: SOPR-IRR -100.V1

Effective Date: July 10, 2016

# **PURPOSE:To outline activities required forPolicies on Investigator Record keeping and Record Retention**

**POLICIES:**

The Investigative Site should maintain the trial documents as specified in essential Documents for the Conduct of a Clinical Trial as described in part 8 of ICH/GCP Guidelines and as required by the applicable regulatory requirement(s). The Investigative Site should take measures to prevent accidental or premature destruction of these documents.

An Investigator shall retain records required to be maintained under this part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

Investigative Site should retain records as described in section 312.62 and 312.64 additional records should be obtained as requested by the sponsor. A minimum of the following documents should be obtained for two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued or for what time period is indicated in the sponsor’s protocol or what the governing IRB requests, whatever period of time is longest will be the length of time records will be retained. Records will be retained and stored at an off-site storage facility.

1. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition the unused supplies of the drug under 312.59
2. Case Histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms (which may be stored at the sponsor or CRO’s facility.) and supporting data including for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual’s hospital chart(s), and the nurses notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
3. Demographic information which includes name, date of birth and contact information of subject should be retained.
4. Any other documentation requested by sponsor to be retained should be archived and retained.

# Case Report Form (CRF) Completion

### Overview, Regulatory Support and References:

CRF completion in a timely manner is very important in assessing data and safety of the study. Correct and, “clean” data is vital to the integrity of the study.

* ICH GCP Consolidated Guideline – 4.9.1
* ICH GCP Consolidated Guideline- 4.9.2
* ICH GCP Consolidated Guideline- 4.9.3

# Policies on Case Report Form (CRF) Completion

Policy Number: SOPR-CRF -100.V1

Effective Date: July 10, 2016

# **PURPOSE:To outline activities required forCase Report Form (CRF) completion.**

**POLICIES:**

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRF’s and in all required reports.

Data reported in the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. and audit trail should be maintained); this applies to both written and electronic changes or corrections (see section 5.18.4(n) in ICH/GCP Guidelines). Sponsors should provide guidance to investigators and/or the investigator’s designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor’s designated representatives are documented, necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

CRFs should be completed to the best of the sites ability (i.e. if the site is still waiting on information from the subject, the CRF should be completed with what information is available.) no later than two business days after the occurrence of the study visit or event.

# Source Documentation

### Overview, Regulatory Support and References:

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.

* ICH GCP Consolidated Guideline – 4.9.1
* ICH GCP Consolidated Guideline- 4.9.2
* ICH GCP Consolidated Guideline- 8.3.13

# Policies on Source Documentation

Policy Number: SOPR-SDO -100.V1

Effective Date: July 10, 2016

**PURPOSE:** 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.

**POLICIES:**

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in all required reports.

Source documents cannot be verbatim of a CRF nor a blank CRF copied for the purpose of being used for a source document.

All corrections on CRFs shall be lined through with one line and initialed and dated by the person lining through the error. If necessary, a brief note explaining why the correction was made to the source document should be added. If the error on the source document has been discovered after a CRF has been sent in to the sponsor, an audit trail should be sent to the sponsor explaining the correction. A copy of the communication between the site and the sponsor should be placed with the corresponding source document.

Source Documents are defined as the first place information has been collected on events of interest; these documents may include but are not limited to:

1. Medical Records (from clinics, hospitals, labs, x-ray departments, verbal accounts from study subjects)
2. Autopsy reports
3. Accident reports
4. Pathology reports
5. Progress Notes

## Policies on Site Selection Visits

Policy Number: SOPR-SSV-100.V1

Effective Date: July 10, 2016

**PURPOSE:** To outline activities required for facilitating site selection visits to determine if the proposed study is appropriate for sponsor and site.

**POLICIES:**

A site selection visit will occur within normal business hours and are scheduled ahead of time with the research coordinator(s).

The sponsor or sponsor representative, affiliated with either the pharmaceutical company or Contract Research Organization (CRO), contacts the research coordinator to schedule a visit.

1. Once the visit is scheduled, the research coordinator will contact everyone involved in the visit. This includes: Principle Investigator, and Sub-Investigators.
2. The study coordinator will gather any study related materials that may be needed by the sponsor representative. The study coordinator will arrange for tours of any pertinent departments and gather any information that may be anticipated (examples: brand name of equipment, calibration dates, name of auxiliary staff and CVs). Study coordinator will also reserve conference room for group meetings and arrange any other accommodations that the representative may need while at Investigator Site.
3. The principal investigator will be available during the monitoring visit for any questions or clarification that needs to be made. If the scheduled date of the audit is inconvenient for the principal investigator, the study coordinator may contact the CRA to request rescheduling at a mutually convenient time.
4. The study coordinator will discuss any questions or findings with the sponsor representative and try to resolve the issues as quickly as possible.

## Policies on Site Initiation Visits

Policy Number: SOPR-SIV-100.V1

Effective Date: July 10, 2016

**PURPOSE:** To outline activities required for facilitating site initiation visits (SIV) during the course of a clinical investigation.

**POLICIES:**

Site Initiation visits (SIV) will occur within normal business hours and are scheduled ahead of time with the research coordinators.

The Clinical Research Associate (CRA), affiliated with either the pharmaceutical company or Contract Research Organization (CRO), contacts the research coordinator to schedule a site initiation visit.

1. Once the visit is scheduled, the research coordinator will contact everyone involved in the study.
2. The study coordinator will gather all study related materials that are pertinent to the study and to the initiation visit. The study coordinator will ensure that all study personnel has a current version of the protocol and all personnel has read the protocol thoroughly prior to the SIV.
3. The principal investigator and auxiliary staff will be available during the SIV for required protocol training and to answer any queries. It is the responsibility for the principal investigator to assure all staff on the study team is trained appropriately on the protocol.
4. The study coordinator will ensure that all open queries and outstanding action items are resolved in a timely manner.

# Adverse Events

### Overview, Regulatory Support and References:

Identifying Adverse Events should be an active process and not a passive one. Caution should be utilized so that the pursuit is not active to the extent that the subject experiences placebo effect related to adverse events or falsely reports adverse events in an effort to “please the investigator”. Improved identification and reporting of adverse events at the site level leads to more accurate safety profiles for Sponsors to make development decisions, regulatory agencies to make approval and labeling decisions and healthcare professionals to make treatment decisions. Without a reliable and valid adverse event profile generated during the research process, large numbers of future patients are put at risk.

Most importantly, information on adverse events should be communicated in appropriate timeframes so that subjects (or their representatives) that are currently enrolled in the protocol are informed of any newly discovered risk that either they or others have experienced. This shows respect for persons and beneficence.

Finally, scientific integrity should be maintained but not to the point that subjects may be harmed. Actions such as “breaking a blind” or withdrawal from the protocol should be considered based on individual circumstances.

* 21CFR312.64(a); 312.64(b); 312.66
* FDA Form 1572: Section 9 ([http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf](http://www.fda.gov/opacom/morechoices/fdaforms/fda-1572.pdf))
* FDA: “The Clinical Impact of Adverse Event Reporting” (<http://www.fda.gov/medwatch/articles/medcont/postrep.htm>)
* ICH Harmonized Tripartite Guideline E6: Good Clinical Practice: 4.3.2, 4.7 & 4.11 (<http://www.fda.gov/cder/guidance/959fnl.pdf>)
* Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events January 15, 2007 (http://www.hhs.gov/ohrp/policy/advevntguid.html)
* Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection (January 2009) (http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2007-D-0202-gdl.pdf)

## Identifying, Handling and Reporting AEs

Policy Number: SOPR-AE-100.V01

Effective Date: PROPOSED July 10, 2016

**PURPOSE:** Information on any adverse experiences of subjects should be identified, documented, reported as a study finding and evaluated as part of the risk/benefit ratio for the continuance of the study. Throughout this process, the subject’s well-being should be maintained.

**POLICIES:**

1. Principal Investigators and/or their designees should gather information from subjects about adverse subject experiences during and between visits.
   1. Subjects should be encouraged, not discouraged, in reporting adverse events.
   2. To help prompt the subject’s memory, questions should not be too vague or open-ended (i.e. “Have you seen a doctor since our last visit?” or “have you taken any pills since our last visit?” instead of “Have you been feeling ok?”).
2. Investigators and/or their designees should actively supplement the subject’s reported information about any potential adverse subject experiences during and between visits with information from other reliable and available sources (e.g. subject’s spouse (if authorized by the subject in writing), hospital/clinic medical records).
3. No adverse event should be ignored, no matter how seemingly insignificant. It may be the onset of a more clinically significant pathology.
4. Any Adverse Events found should be documented consistently in both source documents and research Case Report Forms.
5. Reporting of Adverse Events to Sponsors should favor “Over-Reporting” as opposed to “Under-Reporting”. If there is ever a question as to if an event should be reported to a Sponsor, the answer will always be that it should.
6. Events classified as Serious Adverse Events are reported to both the Sponsor and IRB according to their accelerated timeframe. Note, unless otherwise specified by the IRB, the IRB does not need to be informed unless the Serious Adverse Event is also both Unexpected and Related to the study.
7. Absent any timeframe by the IRB or Sponsor, the default timeframes to report are as follows:
   1. Serious Adverse Events
      1. To the Sponsor: Within 24 Hours of Being Notified
   2. Adverse Events:
      1. To the Sponsor: Documented to CRFs within 3 business days
   3. Unexpected Adverse Events
      1. To the Sponsor: 10 working days (if not SAE)

7.4 Serious Unexpected and Related SAEs

7.4.1. To the Sponsor: Within 24 hours of being notified

7.4.2. To the IRB: Within 5 days of being notified

### Procedure for Identifying Adverse Events

1. At each study visit, the subject should be sufficiently asked if they have or had any adverse events. Documentation of this discussion should be in the source documents, even if not required by the Sponsor.
2. Additional sources of adverse events should be sought when available. Examples include:
   1. Inpatient studies should have the medical record carefully checked every day for new information.
   2. Significant others should be consulted when available (if subject has authorized in writing that it is ok to speak to significant other).
   3. Clinical Observations
   4. Subject Diaries that may conflict with oral statements (each adverse event notation should be initialed and dated by study staff).
3. Sponsors or IRBs use various forms to detail the documentation of an adverse event. To prepare for case report form documentation, source documentation should strive to include the following:
   1. Date/Time of onset
   2. Circumstances preceding onset (e.g. meal, activity etc.)
   3. Severity
      1. Mild: Experiencing mild discomfort with insignificant changes in daily activity or clinical status.
      2. Moderate: Makes accommodating changes in normal daily activity but can still function relatively well. Noticeable changes in clinical status.
      3. Severe: Makes major changes in (or is prevented from accomplishing) normal daily activity. Major changes in clinical status.
   4. Narrative of Progression
   5. Date/Time of resolution (if applicable)
   6. Association with Investigational Drug/Device/Procedure as determined by the Principal Investigator.
4. This documentation should be consistent between the research records and in source documents.

### Procedure for Handling Adverse Events with the Subject

1. Upon identification of an adverse event:
   1. The medically necessary treatment should be determined with the subjects’ best interest in mind.
   2. The determination must be based as to whether to continue or discontinue the subject in the study.
2. The subject should be informed when medical care is needed for concurrent illness(es).
3. Whenever appropriate, treatment within the limitations of the protocol should be exhausted first, unless the subject wishes to withdraw from the protocol.
4. Where necessary to eliminate apparent immediate hazards, the protocol may be deviated from for the benefit of the subject.
   1. The Sponsor AND IRB must be notified of the protocol deviation.
   2. The Principal Investigator should determine if the subject should be removed from the protocol.
5. The Medical Monitor of the Sponsor, if available, may be enlisted to aid in the treatment, particularly in an actively treated SAE.
6. All AEs should be followed until resolved, referred or determined permanent.

### Procedure for Unblinding Investigational Products

1. CRITERIA: Every effort should be maintained to protect the blind unless there is a medical emergency and:
   1. The treating physician needs immediate knowledge to optimize the clinical management
   2. The clinical management would be a different course of action depending on the results of the unblinding (example, in an overdose situation, if the course of action would be the same if the subject were on Drug A versus Drug B, unblinding may not be necessary).
2. Whenever medically permissible, the Sponsor should be notified before the blind is broken.
3. The protocol should dictate the manner in which the blind is able to be broken. In the absence of such explanation, the Sponsor’s policies or prudent practices should dictate the manner in which the blind is broken. Examples are as follows:
   1. Peel Off Labels
   2. Scratch-Off Labels
   3. Interactive Voice Response Systems (IVRS)
4. The blind should only be broken for the subject at hand.
5. In the absence of a medical emergency, the unblinding should only occur in accordance with the protocol.
6. The investigator should promptly document and explain to the Sponsor any premature unblinding of the investigational product(s) with consideration for the criteria above.

### Procedure for Reporting Local AEs and SAEs

1. DEFINITION: A Local Adverse Event is one that occurs to a subject enrolled at our facility.
2. The PI must determine if the event is classified as a Serious Adverse Event (defined in this policy).
3. The event must be reported within the relevant timeframe.
   1. If a Serious Adverse Event,
      1. The immediate report (Note: a more detailed report will promptly follow) to the Sponsor (and the IRB if also unexpected AND related) within the sooner of their timeframes or those stated by this policy.
      2. The more detailed report shall follow upon resolution of the event or as requested by the Sponsor or IRB.
      3. Reports to Sponsors and IRBs do not alleviate Investigative Site of their responsibility for following any other clinic or hospital policies for reporting adverse events.
   2. If not a Serious Adverse Event, then the information must be reported according to IRB policy (usually at Continuing Review time) and Sponsor policy (usually just documentation on the CRFs).
4. The mechanism for reporting shall vary according to Sponsor and IRB policy.
5. For external reporting, Subjects should only be identified by their code or other de-identified manner unless necessary and allowed for under the privacy and confidentiality laws.
6. In the event the Principal Investigator believes the Informed Consent Document should be modified but if the Sponsor or IRB denies this request, the Institutional Official should be contacted for guidance.

## Handling Information on Adverse Events from External Sources

Policy Number: SOPR-AE-110.V01

Effective Date: Proposed July 10, 2016

**PURPOSE:** Adverse experiences often occur with the use of the Investigational Product at other research sites or in the worldwide market. This information should be considered in the risk/benefit ratio of any study activity.

**POLICIES:**

1. The site accepts information from all sources that may have bearing on the safety of the subjects. Most commonly, these come in the form of:
   1. IND Safety Reports from the Sponsor (a.k.a. Medwatch Reports)
   2. News and Journals related to the study intervention
2. MD Trials shall note any Sponsor and IRB thresholds for reporting (noting that many IRBs only require reporting adverse events that meet all three definitions of serious, unexpected and related to the study) as well as any timeframes.
3. Unless a sooner reporting timeframe is requested by the IRB or Sponsor, the suggested timeframes to report are as follows:
   1. Serious Adverse Events
      1. To the Sponsor: Within 24 Hours of Being Notified
      2. To the IRB: Within 24 Hours of Being Notified
   2. Adverse Events:
      1. To the Sponsor: Documented to CRFs within 3 business days
      2. To the IRB: At time of continuing review but not to exceed annually
   3. Unexpected Adverse Events
      1. To the Sponsor: 10 working days (if not SAE)
      2. To the IRB: 10 working days (if not SAE)
4. In the event that a Sponsor has submitted to the IRB on the Site’s behalf, a copy of such submittal should be kept in the study’s Regulatory Binder.
5. MD Trials has the right to terminate participation in a study if the new information causes concern for subject safety.

### Procedure for Processing External AEs and SAEs

1. The Principal Investigator should review the information and consider if a change in the protocol, consent form or other study activity is desired. If so, this request should be submitted to the Sponsor and IRB for approval.
2. Any additional procedures to follow or forms to be completed will generally follow the policies of the IRB and Sponsor/CRO.
3. The information source (i.e. copy of the IND Safety Report) along with any confirmation of receipt by the Sponsor and/or IRB shall be stored in the study files (i.e. in the Regulatory Binder). A letter stating that the information was submitted to the IRB by the Sponsor on the site’s behalf is evidence of submittal to the IRB.
4. In the event that the Principal Investigator believes the Informed Consent Document should be modified but the Sponsor or IRB denies this request, the Institutional Official should be contacted for guidance.

## Research Material Confidentiality

Policy Number: SOPR-CRI-100.V1

Effective Date: July 10, 2016

**PURPOSE:** The relationship between the Sponsor and Conduct Clinical Trials and its Partner Sites is based on the trust that proprietary information disclosed to Conduct Clinical Trials will only be used as necessary to establish feasibility to conduct and/or to conduct the study. Situations arise, however, when the information needs to be disclosed by Conduct Clinical Trials to a third-party for reasons that may or may not be related to the conduct of the study.

**POLICIES:**

1. Prior to the beginning of a study involving a proprietary product, it is customary that an agreement addressing confidentiality of the Sponsor’s information be signed between Conduct Clinical Trials/Partner Sites and the Sponsor. This is known as a Confidentiality Agreement (CA), Non-Disclosure Agreement (NDA), Confidential Disclosure Agreement (CDA) or some variant thereof. Any conflict between this policy and one of these agreements shall be governed by the contractual agreement to the extent permissible by law.
2. Information covered in this policy is any item containing the following:
   1. Sponsor’s Name
   2. Protocol (including the title and/or number)
   3. Informed Consent Form
   4. Information of the investigational product (including its name and supporting documentation such as an Investigator’s Brochure or other non-public documentation)
   5. Any other information given under the auspices of confidentiality
3. In the absence of a Confidentiality Agreement or in the presence of a more lenient one, Conduct Clinical Trials and Partner Sites shall be at a minimum:
   1. Only discuss the study with the following:
      1. Sponsor company
      2. Fellow Employees on a need-to-know basis
      3. Representatives of the IRB
      4. Representatives of the FDA, OHRP or other regulating entity
      5. Potential subjects. NOTE: Unless inconsistent with any written Sponsor confidentiality agreement, copies of unsigned consent forms should be allowed to be taken home by prospective subjects. If they do not enroll in the study, reasonable efforts are to be done to ensure the consent form is returned to the study site to prevent accidental disclosure.
   2. Not using the information for purposes other than the intent to establish feasibility to conduct or to conduct the study (i.e. investment/in licensing recommendations, research & development decisions, and interviews with reporters/financial analysts etc.).
4. Although a Sponsor may call for the return or destruction of confidential information, Conduct Clinical Trials must allow contractually for the maintenance of at least one copy of the material for historic purposes for the length of time dictated by Facility policy, even if the study was not undertaken.

### Procedure for Obtaining Confidentiality Agreements

1. Submit proposed contract to the reviewing entity per corporate policy.
2. Allow reviewing entity to make disposition determinations which may include one the following:
   1. Submit to Sponsor a previously agreed contract that would govern the release (i.e. a “Global CDA”);
   2. Submit to Sponsor requested changes to the CDA;
   3. Approve the CDA.
3. Maintain in good faith any information submitted to Facility in conjunction with the CDA (i.e. Protocol Summaries) with the expectation that the CDA will be signed.

### Procedure for Release of Information to Third Parties

1. Review the Confidentiality Agreement and other written instructions from the Sponsor. Usually this will allow for disclosure on an “as needed” basis to:
   1. Research staff
   2. CRO
   3. IRB
   4. FDA, OHRP or other governing authority
   5. Other entities directly involved with the conduct or approval of the study (i.e. medical executive boards, pharmacy committees etc.).
2. If needed pursuant to the conduct of the study, a request for Confidentiality Agreement between Conduct Clinical Trials and the potential recipient (i.e. a potential sub-contractor) must be made to the Institutional Official unless one of the following is true:
   1. The recipient is also party to (or covered under) Conduct Clinical Trials Confidentiality Agreement with the Sponsor
   2. The Sponsor has a separate Confidentiality Agreement with the potential recipient
3. If disclosure is required pursuant to a court order, the Sponsor should be notified as soon as possible to allow for them to utilize their own legal resources to prevent the disclosure if they deem it appropriate.
4. Any other requests for disclosures (media, physicians not involved in the study) should be directed to the Sponsor for disposition. If the Sponsor opts for us to disclose the information, this will be obtained in writing prior to disclosure.
5. Whenever possible, proprietary information not needed in the disclosure should be redacted.

### Procedure for Redacting Study Documents for Release

1. Make a paper copy of the original. If the original is electronic, print the document (do not send the document in its electronic form as word processing tools such as “Track Changes” make it difficult to completely alter an original document. This is referenced as the “First Copy”.
2. Read the First Copy and render unreadable with a thick black pen any information that is considered confidential as spelled out in said policy and the Confidentiality Agreement.
3. Note any information that may be a HIPAA identifier and redact those elements per that policy.
4. Note any information that may be proprietary to Conduct Clinical Trials (i.e. business practices, referral sources, financial information etc.) and redact per policy or under advisement of the CEO.
5. Once all information is fully blacked over, make 2 copies (“Second Copies”) of the document. This prevents the blacked-out information from being readable from the backs of pages.
6. Proof the Second Copies so that no redacted information can be deciphered.
7. Shred the First Copy, send one Second Copy and keep one Second Copy for the files noting whom it was disclosed to and when.

## *Direct Advertising for Study Subjects*

Policy Number: SOPR-RCRT-130.V01

Effective Date: July 10, 2016

**PURPOSE:** Direct advertising for research subjects (i.e. advertising that is intended to be seen or heard by prospective subjects) may be an effective means of communicating the availability of the study to a large population. Direct recruiting, advertisements are seen as part of the informed consent and subject selection processes. Conduct Clinical Trials and Investigative Site shall take the necessary steps to ensure that the information presented in print, radio, television, internet of other media advertisements are not misleading to subjects and conform to both the FDA and the NIH Office of Human Research Protections standards as interpreted by the IRB.

**POLICIES:**

1. Investigative Site may freely disclose/advertise without IRB approval that they are generally involved in research or conducting research.
   1. These ads must be generalized to the presence of research or clinical trials at Investigative Site.
   2. Under no circumstance may these “general ads” refer to specific studies regardless if the study is completed, in-progress or expected to begin. This includes but is not limited to the following:
      1. Medications being tested
      2. Inclusion/exclusion criteria
      3. Naming Sponsors
      4. Stating patient stipends are available
2. Advertisements intended for recruiting subjects for protocols shall be objective and non-coercive. The below criteria shall be met:
   1. Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest. Suggested items are:
      1. The name and address of the clinical investigator and/or research Facility.
      2. The condition under study and/or the purpose of the research.
      3. The person or office to contact for further information.
      4. In summary form, the criteria that will be used to determine eligibility for the study.
      5. A brief list of participation benefits, if any.
      6. The time or other commitment required of the subjects.
      7. That subjects will be paid, but should not emphasize the payment or the amount to be paid.
   2. The ads should not contain:
      1. Statements implying a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
      2. Language conforming to the policy on referencing investigational products in public (i.e. not promising “new” or “safer” therapies).
      3. A promise of "free medical treatment," when the intent is only to say subjects will not be charged for taking part in the investigation. If the ad intends to promote that study-related medical care will be provided at no cost, then this should be clearly described.
   3. The relative font sizes used as well as other visual/audio effects are not to be coercive in nature.
      1. Audio/visual effects shall not be utilized to emphasize the benefits of participation or payments.
      2. Audio/Visual effects shall not be utilized to de-emphasize the risks of participation.

### Procedures for Obtaining Pre-Approval of Media

1. Conduct Clinical Trials shall, early on in the process, invoke its usual media approval and/or purchasing process in proceeding with the project and for final approval of the advertisement.
2. Prior to the submittal of any printed ads to a publication agency (e.g. newspaper, journal, and Web Site host) Conduct Clinical Trials shall have written verification that the IRB has approved such ad.
   1. This verification shall be in writing and on the letterhead of the IRB.
   2. The verification shall have an attached copy of the ad.
3. Prior to the submittal of any taped ads (e.g. radio, TV) to a media agency, MD Trials shall have written verification that the IRB has approved such ad.
   1. It is encouraged (particularly if Conduct Clinical Trials is underwriting the cost of developing the ads) that the IRB review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate content.
   2. The IRB should review the final audio/video tape.
   3. This verification shall be in writing and on the letterhead of the IRB.

### Procedure for Internet Study Database Listings

1. Confirm that the internet listing agency’s format molds to the FDA Guidance on this topic: that of “the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information.”
2. If fitting the format, although the FDA does not require IRB review, the IRB and/or Sponsor may require review of the listing. Listings on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) are designed to meet this exclusion from the requirement of IRB review.
3. Those listings not meeting this exclusion should obtain documentation of IRB approval to list as evidenced by either standing permission from the IRB (i.e. in the Formal Agreement) or a study specific listing.
4. Review the final posted listing to make sure it molds to the format acceptable.

## *Pre-Screening and Screening/Enrollment Logs*

Policy Number: SOPR-RCRT-170.V01

Effective Date: July 10, 2016

**PURPOSE:** Prescreening and Screening/Enrollment logs may be kept to reflect study activity by demonstrating that active recruitment efforts are being made as well as provide evidence that we are screening out individuals who do not fit the criteria of the study. These logs can also provide useful feedback to the Sponsor and/or the institution on common reasons why people are not enrolling or not eligible to enroll in the study.

**POLICIES:**

1. When Pre-Screening logs are kept reflecting activity on those individuals prescreened but not consenting to the protocol, they usually contain information; de-identified information describing the individual (e.g. “48WF”) and reasons for refusal. In the rare event that identifiers are needed, this would require a HIPAA Authorization (or a waiver of such authorization) from the pre-screened subject.
2. Screening/Enrollment logs are often kept for logging individuals who consent to reflect those that either screen-failed or otherwise progress through the protocol. Usually an Authorization is obtained as part of the consent process; thus, this may obtain identifiers if allowed in the authorization.
3. Privacy policies apply to content and security of information contained in the Pre-Screening Logs as well as Screening logs. NOTE: if this information is not encrypted, it may be considered “unsecured PHI” which is subject to significant penalties. Refer to any Facility policy on unsecured PHI.
4. Conduct Clinical Trials or Investigative Site may either create their own logs or use a Sponsor supplied logs.

### Procedure for Disclosing Pre-Screening Logs to Sponsor, IRB or Regulators

1. Ensure the document does not contain Protected Health Information, or that the documentation and release of any PHI is allowed via HIPAA authorization(s) or waiver of authorizations.
2. If the document contains PHI to be redacted for release, any identifiers should be redacted such as in the following manner:
   1. Make a paper copy of the original. If the original is electronic, print the document (do not send the document in its electronic form as word processing tools such as “Track Changes” make it difficult to completely alter an original document. This is referenced as the “First Copy”.
   2. Read the First Copy and render unreadable with a thick black pen any information that is considered confidential as spelled out in said policy and the Confidentiality Agreement.
   3. Note any information that may be a HIPAA identifier and redact those elements per that policy.
   4. Note any information that may be proprietary to Conduct Clinical Trials (i.e. business practices, referral sources, financial information etc.) and redact per policy or under advisement of the CEO.
   5. Once all information is fully blacked over, make 2 copies (“Second Copies”) of the document. This prevents the blacked-out information from being readable from the backs of pages.
   6. Proof the Second Copies so that no redacted information can be deciphered.
   7. Shred the First Copy, send one Second Copy and keep one Second Copy for the files noting whom it was disclosed to and when.
   8. If the document with PHI is in electronic form, the PHI should be deleted before being electronically transferred. The de-identified document should be saved and sent in a password protected PDF file.

### Procedure to Handle Requests to Withdraw

1. If the request comes from a source other than the subject or their legal guardian:
   1. The person’s concerns should be heard
   2. Any misinformation should be clarified (this may be misinformation on the part of the requestor OR the researcher)
   3. The requestor should be reminded that the subject has the right to informed self-determination and that their concerns should be taken up with the subject themselves.
   4. The requestor has the right to bring their concerns to a Medical Staff Peer Review or an Ethics/Compliance official
2. If the request comes from the subject/guardian
   1. The core concerns should be heard and addressed if possible (i.e. requesting removal from a psychiatric protocol because they cannot tolerate the regular unit’s smoking schedule could otherwise be addressed by allowing extra smoking time for them)
   2. If the concerns are otherwise not permissible by the protocol or result from additional anxiety or adverse events, some encouragement is appropriate but not to the point where it is coercive. Additionally, the subject should be reminded of any procedures/timelines for orderly withdrawal from the protocol so that the Principal Investigator may make an informed decision.
   3. If the subject is persistent and the Principal Investigator has not been notified, they should be notified at this time.
   4. If the subject is persistent with the Principal Investigator, the PI should engage the Sponsor’s procedures to withdraw the subject from the study.
   5. If the subject is persistent and the PI does not withdraw them from the study, the matter should be brought to the attention of the Medical Director or an Ethics/Compliance officer.

# Privacy of Protected Health Information in Research

### Overview, Regulatory Support and References:

Each person has an inherent right to the privacy of their personal information, especially Protected Health Information (PHI) or other information that may be considered sensitive. Research, however, is dependent on the release of information to individuals that may not have the legal obligation or safeguards to protect confidentiality customarily found in a healthcare setting. Therefore, when disclosing data that can identify an individual, the individual should know who will receive their data, what data is needed, when it will be released (or no longer released) and any other information surrounding the further use and disclosure of their data. With that knowledge, the individual may give their written authorization to release the data necessary to do the research.

Many times, the information needed is considered de-identified in accordance with the HIPAA Privacy Rule, thus the individual’s authorization to disclose the information is not required. Other times, the requirement for a written authorization may be waived by an Institutional Review Board (IRB) or Privacy Board according to criteria set forth in HIPAA given the amount of additional protections for the privacy of the data over the level of risk. In consideration of this, federal laws pose certain criteria under certain circumstances for the release of PHI without the individual’s written authorization.

There are a limited number of ways to disclose data for research purposes depending on the situation. The criteria depends on the detail of data needed (*i.e.,* identifiers vs. no identifiers), presence of the data at the time of need (*i.e.,* retrospective versus prospective), risk and other factors. While many disclosures will require an authorization, there are many that do not. Laws for the release of information without such authorizations are designed for situations where authorization is not practical, but there are enough protections in place that render a low risk to the individual even if re-identified.

* 45C.F.R. 164.502(a)(1)(i), 164.502(a)(1)(iv), 164.508, 164.512(i), 164.514(a), 164.514(b), 164.514(e)
* NIH’s “Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule” (April 14, 2003) [http://privacyruleandresearch.nih.gov/pdf/HIPAA\_Booklet\_4-14-2003.pdf](http://privacyruleandresearch.nih.gov/pdf/hipaa_booklet_4-14-2003.pdf)
* NIH’s “Clinical Research and the HIPAA Privacy Rule” (February 5, 2004) <http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf>
* Guidance for Industry: IRB Review of Stand-Alone HIPAA Authorizations Under FDA Regulations ([http://www.fda.gov/OHRMS/DOCKETS/98fr/03d-0204-gdl0001.pdf](http://www.fda.gov/ohrms/dockets/98fr/03d-0204-gdl0001.pdf))

# Accountability of Investigational Products

### Overview, Regulatory Support and References:

* ICH Harmonized Tripartite Guideline E6: Good Clinical Practice:
* Poison Prevention Protection Act (15 U.S.C. 1471-1476) (Public Law 91-601, 84 Stat. 1670, December 30, 1970, as amended)
* Title 16--Commercial Practices / CHAPTER II--CONSUMER PRODUCT SAFETY COMMISSION/PART 1700--POISON PREVENTION PACKAGING
* U.S. Consumer Product Safety Commission June 22,2000 Letter to Canon Communications, LLC “RE: Drugs dispensed for household use in clinical trials” ([http://www.cpsc.gov/BUSINFO/trials.pdf](http://www.cpsc.gov/businfo/trials.pdf))

# Site Transfer Investigational Product (IP) Form

INSTRUCTIONS FOR TRANSFERS:

1. Properly complete all sections

2. Type or print all information – one transfer per page; one protocol per page

3. Enter signature of individual preparing IP and receiving IP

4. Pack the IP well to minimize breakage and leakage for transfers

5. All IPs must be transferred per sponsor specifications for handling/transport

6. Enclose the completed list with the IP

7. Ensure IP Transfer is conducted per SOP

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IP Transferred From

Name of Institution:

Street Address: City/State/Zip Code

IP Transferred To

Name of Institution:

Street Address: City/State/Zip Code

Sponsor:

IP Name:

Quantity (include units):

Lot/Serial Number or Other Identifier:

Comments:

Departure Date/Time: Staff Name \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Departure Temp:

Arrival Date/Time: Staff Name \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Arrival Temp: Per Protocol Specifications: Yes No (if no add comment)

Comments:

Reason for Transfer: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Principal Investigator Signature/Date:

# SOP: Transportation of IP Between Satellite Sites:

**PURPOSE:** To clarify the responsibilities and procedures of the transportation of IP between satellite sites.

**III. DEFINITIONS**

**INVESTIGATIONAL PRODUCT (IP):** "Investigational product" is defined as any unapproved drug, medical device, or biologic undergoing clinical trials to provide evidence to regulatory authorities that the product is safe and efficacious. Synonymous with term **INVESTIGATIONAL DRUG**, further defined as "...a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.” *(ICH GCP E6, section 1.33*)

**RESPONSIBILITIES:**

1. Investigational Site Responsibilities
2. 1. The Main Site is responsible for accurate and timely transport of IP between the main site and satellite sites, as outlined in the procedures section of this SOP.

**PROCEDURES:**

Drug is transported under study article storage requirements. (i.e.: in cooler with ice pack(s) if refrigeration is required). Transportation from the Investigational Pharmacy location to the various satellite pharmacy locations listed above will generally take less than one hour (but up to 2-hour time frame is allowed). TRANSPORT of IP requirement of being frozen during transport will not be eligible for transport to a satellite pharmacy.

Upon receipt of study articles at the satellite pharmacy, the responsible STUDY COORDINATOR OR DESIGNEE will reconcile the shipment and ensure temperature was maintained per protocol requirements.

## Accountability Logs For Investigational Products

Policy Number: SOPR-AIP-110.V1

#### Effective Date: July 10, 2016

**PURPOSE:** For studies involving the receipt, inventory, dispensing and disposal of Investigational Products, there should at all times be a current accounting of the Investigational Product inventory.

**POLICIES:**

1. Investigative Site is to maintain adequate records of the dispensing, current inventory and disposition (including return or destruction) of Investigational Product including dates, quantity, use by subjects, final return/destruction and other fields required by the protocol or state law.
2. Such accountability logs shall be maintained in accordance and for the duration of the record retention policy.
3. Any discrepancies are to be followed up until resolved or documented as unaccounted for.
4. Investigative Site may use their own or a Sponsor’s form(s).

### Procedures upon Receipt of Investigational Product from Sponsor

1. Receipt of Investigational Product should be documented (i.e. in an Accountability Log), which may be a site or Sponsor generated form. Customary fields include:
   1. Date of Receipt
   2. The unique identifiers (including any Lot/Serial/Randomization numbers)
   3. Quantity Received (note, if drug bottles are sealed, “sealed bottle” shall suffice)
2. Physical examination of the packaging should search for the following:
   1. The statement “Caution: New Drug (Or Device)- Limited by U.S. Law to Investigational Use” or similarly required FDA statement
   2. An expiration date, if appropriate
      1. If the date is not labeled on the container but in the form of a letter, it should be handwritten on the container unless otherwise directed not to do so by the study Sponsor
      2. A statement from the Sponsor that they will maintain the expiration date shall suffice in lieu of having a documented date
3. Any discrepancies or errors should immediately be documented and reported to the Sponsor.

### Procedures for Logging Administration/Dispensing of Investigational Product to Subjects

1. For Hospitals, normal hospital policies must be followed (which may include a “Home-Medication” or “self-administered” policy) and supersedes this policy.
2. Each time an Investigational Product is administered or dispensed to a subject, the Accountability Log should be updated with the following information:
   1. Date dispensed/administered
   2. Any unique identifier(s) of the administered/dispensed product (Lot/Serial/Randomization/Visit etc.)

### Procedures for Logging Return of Investigational Product to Investigative Site:

1. Each time an Investigational Product is returned, the Accountability Log should be updated, usually with the customary information such as:
   1. Date of return
   2. Any unique identifier(s) of returned product (Lot/Serial/Randomization/Visit etc.)
   3. Quantity returned with as much detail as possible
      1. For example, for pills dispensed in a bottle, “6 pills returned” would suffice
      2. For example, for pills dispensed in a blister pack, “3 pills returned pertaining to Day 3 AM, Day 7 PM and Day 8 AM” would suffice.

### Procedures for Logging the Return-To-Sponsor/Destruction of Investigational Product

1. When Investigational Product is returned to the Sponsor or destroyed, the Accountability Log should be updated with the following information:
   1. Date of return/destruction
   2. Unique identifier(s) of returned/destroyed Investigational Product
2. All other procedures in this area are to be followed.

### Procedures for Inventory Discrepancies

1. When a discrepancy occurs between the physical count and the logs, documentation of such will be completed in the study files.
   1. Date discrepancy is noticed
   2. Narrative of attempts to reconcile
   3. Resolution of reconciliation
2. For inpatient pharmacies, other reporting may be necessary based on local pharmacy policy.
3. A Protocol Deviation should be documented pursuant to that policy as well as notifying any external parties as required (Sponsor, IRB etc.).
4. Information concerning product(s) that is unaccounted for should be logged with sufficient detail so that there maintains an accurate inventory (example “Missing 2 bottles (V3 and V4)” instead of “missing bottles”).

## Storage of Investigational Product

Policy Number: SOPR-AIP-120.V1

Effective Date: PROPOSED July 10, 2016

**PURPOSE:** Storage of Investigational Products shall maintain the integrity of the Investigational Product as well as to prevent accidental release for which it is not intended.

**POLICIES:**

1. Physical storage requirements include “Double-Lock” conditions
   1. Limited access through the first lock preventing non-research/non-administrative staff from access
   2. Second lock shall be in form of an affixed or substantially constructed container/cabinet/refrigerator etc.
   3. Access through the second lock should be limited to study staff.
2. Investigational Products should be stored within the temperature requirements of the Protocol or, in the absence of Protocol-driven instructions, other authoritative documents such as written instructions from the Sponsor. Any conflicts between documents relating to storage requirements should be resolved in writing by the Sponsor.
3. A Sponsor, IRB, IBC or other relevant organization may impose additional storage requirements and these are also to be documented as to how they will be followed. Any conflicts between documents relating to storage requirements should be resolved in writing by the Sponsor.
4. In the event that the Investigational Product is stored on a patient unit (i.e. medication room, dispensing machine), the container with the Investigational Product will be identified and temperature logs are to be kept as required.
5. When relocating Investigational Products, the storage specifications in regards to temperature shall be maintained throughout the move. This shall be documented in either temperature logs or other Note to File.
6. Other requirements for storage by the Sponsor/IRB/IBC/etc. (e.g. humidity logs, rodent/insect protection plans etc.) will be documented accordingly.

### Procedure for Temperature Control and Logs

1. A Temperature Log shall be kept at all times the product(s) are stored, regardless of the temperature range (i.e. even if required to be stored at “room temperature”, documentation that the temperature remained in an ambient range is necessary). Note that this may be accomplished via a thermometer that has controlled temperature monitoring or electronic storage that is downloadable. The log shall, at a minimum:
   1. Be labeled and proximal to the storage medium (i.e. taped on or above the freezer, by the cabinet etc.) so that it is not confused with other logs.
   2. Shall specify in each case or at the top of the page whether the temperature’s scale is Centigrade (C) or Fahrenheit (F).
   3. Documented on at a frequency required by the Protocol or, in the absence of protocol-specific instructions, consistent with usual clinical practice.
2. If Investigational Products are to be stored at a temperature other than room temperature (i.e. refrigerated), then a backup system should be in place in the event of power failure. Examples of this can be the following:
   1. The preferred method is connecting the refrigerator to a “generator” outlet
   2. Separate cooler that could maintain the temperature range
   3. Moving the Investigational Product to another similarly secure location while maintaining the storage conditions during transport
3. Copies of the relevant Temperature logs can be placed in study folders upon archiving so that the study documents can be complete.
   1. In the event that one log is kept and is to be used for multiple studies, a copy of the log for each day of an active study should be filed with the study so that the packaged study is a “complete set” of documents.
4. Any time a product’s storage conditions exceeds the parameters required by the Protocol or other written instructions, the Sponsor should be promptly notified for further instructions. A protocol deviation report may also be necessary.

## Return-To-Sponsor or Destruction of Investigational Product

Policy Number: SOPR-AIP-150.V1

#### Effective Date: July 10, 2016

Purpose: Investigational Products should not be maintained in inventory when their use is no longer anticipated.

**Policies:**

1. When it no longer becomes necessary for the Facility to keep an inventory of the Investigational Product, it shall be returned to the Sponsor or destroyed. Examples of such times would include:
   1. The Study is completed or discontinued.
   2. The Investigational Product has expired.
   3. The Investigational Product is damaged, returned by a subject or otherwise unfit for use.
2. Returning the Investigational Product to the Sponsor shall be the preferred method of clearing out the inventory as opposed to alternative methods of disposal.
3. In the event the Sponsor desires that the Investigational Product be disposed of by MD Trials as opposed to being returned, it shall be done according to the Sponsor’s written request provided it comply with all applicable federal, state, local laws and other relevant Site policies.

### Procedure for the Return of Unused Investigational Product

1. Documentation shall be maintained concerning the return of the Investigational Product which shall contain:
   1. The quantity of the Investigational Product returned; AND
   2. In the event the Investigational Product is packaged with identifiers on it (e.g. serial number or randomization number), the documentation shall reflect such detail; AND
   3. The date and manner of shipment (i.e. FedEx, picked up by Sponsor etc.); AND
   4. Confirmation that the shipment was received; AND
      1. Written confirmation shall be in the form of a written acknowledgement of receipt by the company or a copy of the signed receipt from the shipping company; AND
      2. Verbal confirmation (as occurs when a study monitor collects the product and is not prepared to give a written statement), although not preferred, is acceptable when documented as to the date, time and person spoken to and is emailed to both the study Sponsor and the monitor.
2. In the event the product is shipped (as opposed to being picked up by the Sponsor);
   1. The manner of shipment shall have a mechanism of being traced.
   2. In the event the Sponsor does not receive the shipment within a reasonably expected timeframe, Investigative Site shall take the necessary actions with the shipping company to locate the package and have it delivered appropriately.

### Procedure for the Disposal of Unused Investigational Product

1. To dispose of investigational product(s), Investigative Site should first attempt to receive, in writing, documentation specifically stating that the Sponsor does not wish to have the unused Investigational Product returned to them AND the method the Sponsor wishes to have the Investigational Product disposed of. This request shall be stored in the appropriate location in the study binders.
2. Documentation shall be maintained concerning the disposal of the Investigational Product which shall contain:
   1. The quantity of the Investigational Product disposed of; AND
   2. In the event the Investigational Product is packaged with identifiers on it (e.g. serial number or randomization numbers), the documentation shall reflect such detail; AND
   3. The date and manner of disposal; AND
   4. The staff member or company who conducted the disposal; AND
3. A copy of this documentation shall be sent to the Sponsor and kept with the research records.

# Laboratory Process

### Overview, Regulatory Support and References:

Laboratory work is often performed in the clinical research setting. All equipment provided should be appropriate for the task. The staff obtaining the specimens should be adequately trained. Specimens should be stored in a manner that maintains the integrity of the specimen until the laboratory can process it. If specimens are shipped to a remote lab, not only must the integrity of the specimen be maintained throughout the varying shipping time and handling conditions, but it must be appropriately packaged and labeled as it will be transported via public highways and/or airways. All of this is necessary to protect a) the subject from unnecessary redraws; b) the data from loss of specimen integrity; c) the research environment/personnel from infections; and d) the general public from accidental exposure.

* 49CFR172.704, 173.196, 173.199
* 49CRF175.10(13) Exceptions/Carbon dioxide, solid (dry ice)
* International Air Transport Association: Packing Instructions 650 (<http://www.iata.org/NR/ContentConnector/CS2000/SiteInterface/sites/whatwedo/dangerousgoods/file/PI650.pdf>)
* 2004 Emergency Response Guidebook Guide 158 (<http://hazmat.dot.gov/pubs/erg/g158.pdf>)
* 2004 Emergency Response Guidebook Guide 120 (<http://hazmat.dot.gov/pubs/erg/g120.pdf>)

## Receipt, Kit Monitoring and Storage of Laboratory Supplies

Policy Number: SOPR-LAB-110.V1

#### Effective Date: July 10, 2016

**PURPOSE:** The chance of unnecessary redraws or other delays in the research process due to insufficient, damaged or expired laboratory supplies should be minimized.

**POLICIES:**

1. Upon receipt of laboratory supplies for a study, the following will be noted:
   1. Any storage environment requirements and in the event that storage conditions are not able to be met, the Sponsor should be contacted as to the disposition of the supplies.
   2. Any expiration dates
2. Lab kits should be logged on the Study Specific Lab kit log (including, study I.D., Study Visit, Study Kit #, and Expiration Date).
3. Upon initial receipt and throughout the study, any missing, damaged or soon to be expired supplies should have a replenishment request initiated with ample time to have it shipped to the site. Sponsors and Central Labs may differ in their request procedures and those procedures should be followed.

## Phlebotomy

Policy Number: SOPR-LAB-120.V1

Effective Date: July 10, 2016

**PURPOSE:** Acceptable phlebotomy practices should be followed with research subjects.

**POLICIES:**

1. For phlebotomy occurring in an inpatient setting, any additional hospital policies should be followed.
2. The Site should follow its own policies independent of this manual on the drawing of blood and the issues that surround it which should include, but not be limited to, the following:
   1. General Phlebotomy
   2. Needle-Stick protocols
   3. Appropriate Training/Licensure of Staff
3. In addition to the reporting requirements of adverse events occurring during phlebotomy required by the Site’s policies, these events may also need to be reported through research-related mechanisms as well (i.e. to the IRB, Sponsor etc.).
4. Storage of specimens prior to transport shall be adequate and monitored.

### Procedure for Storage of Specimens Prior to Transport

1. In the event that sub-ambient temperatures are required for storage,
   1. The storage medium should be prepared for loss of power to protect the integrity of the specimens in the event of such power loss.
   2. A Temperature Log shall be kept at all times the specimens are stored awaiting packaging (i.e. frozen for batch shipment). The log shall, at a minimum:
      1. Be clearly labeled and kept in the temperature log book
      2. Shall specify the temperature scale as Centigrade (C)
         1. Contain the minimum and maximum temperature since the last reading as well as the current temperature. Note: the minimum/maximum temperature should be reset after each reading. Temperatures will not be read on weekends or holidays.
   3. If a sponsor requires more frequent documentation of temperature, a thermometer that records daily temperature or has an electronic, downloadable storage will be added.

## Training Requirements for Packaging and Shipping of Specimens

Policy Number: SOPR-LAB-130.V1

Effective Date: July 10, 2016

**PURPOSE:** Proper training for the packaging and transportation of specimens is beneficial to the safety of our employees and the general public as well as protects the integrity of research specimen(s).

**POLICIES:**

1. Employees shall be trained on packaging specimens in the appropriate classification, identification, packing, marking, labeling, documenting, and arranging for acceptance by a courier for transportation.
2. Employees shall obtain an International Air Transport Association (IATA) certification and assure the certification is current before shipping any bio-hazard materials, including, tissue, plasma, urine, serum or dry ice.

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### Procedure for Training to Package/Transport Category B Diagnostic Specimens (UN3373)

1. All research employees or other employees that may assist in this function of the research process shall complete the most current training module prior to undertaking duties.

### Procedures for Training to Package/Transport Dry Ice (UN1845)

1. Establish if Dry Ice Certification is needed (usually it is not). Dry Ice certification is currently not required when:
   1. Packaged in quantities not exceeding 2.3 kg (5.07 pounds) per package
   2. Packed in packaging designed and constructed to permit the release of carbon dioxide gas to prevent a build-up of pressure that could rupture the packaging
   3. Used as a refrigerant for the contents of the package.
2. The package must be marked according to regulation, specifically with the name of the contents being cooled (e.g. Category B Biological Specimens), the net weight of the dry ice or an indication that the net weight is 2.3 kg (5.07 pounds) or less, and also marked ''Carbon Dioxide, Solid'' or ''Dry Ice''.

# Research Documentation Maintenance

### Overview, Regulatory Support and References:

Research data must be verifiable not only immediately but also have the ability to be re-verified many years in the future. Documentation of the activity and the basis of the data should be accomplished in real-time. The monitoring process shall help give guidance to the site on better ways to verify and recreate the study. Monitors and auditors should have access to the necessary information to fulfill this function. Finally, as the data may be subject to further audits after the study is completed, the study information should be stored in an organized and easily retrievable manner. This also includes the storage of source documents not customarily stored in the research CRFs (i.e. a hospital medical record). Finally, with the growing amount of information being kept electronically, safeguards should be in place to protect the confidentiality and integrity of the information used/gathered.

* 21CFR312.62 Investigator recordkeeping and record retention
* FDA Guidance for Industry (April 1999): Computerized Systems Used In Clinical Trials (<http://www.fda.gov/ora/compliance_ref/bimo/ffinalcct.htm>)
* FDA Guidance for Industry (August 2003): Part 11, Electronic Records; Electronic Signatures - Scope and Application (<http://www.fda.gov/cder/guidance/5667fnl.htm>)

## Retention of Medical Records and Research Records

Policy Number: SOPR-RIM-110.V1

Effective Date: July 10, 2016

**PURPOSE:** Investigative Site recognizes the difference between the medical record (i.e. for treatment) and other source documents/Case Report Forms used exclusively for research. There are also other essential documents that pertain to research protocols that are not patient-related such as regulatory documents. Each must be retained according to policy, law and contractual agreement.

## Storage and Destruction of Paper-Based Research Documentation

Policy Number: SOPR-RIM-130.V1

Effective Date: July 10, 2016

**PURPOSE:** Storage and/or destruction of paper-based research records shall adhere to the appropriate conditions and timeframes, respecting Sponsor and subject confidentiality as well as taking into consideration that the documents may need to be unpacked to recreate the study within a relatively short time period.

**POLICIES:**

1. In the event that on-site shelf space becomes an issue, research records for closed protocols may be stored or destroyed in accordance with both this policy and any other Facility’s policies
2. Storage shall;
   1. Be secure from accidental loss, damage and/or disclosure.
   2. Allow for easy retrieval and recreation of the research activity.
3. Investigative Site shall destroy research-related documents when they no longer remain useful to Investigative Site, the Sponsor AND other regulatory agencies. Destruction shall only be done after the required retention period had ended. In the event that the Investigative Site wishes to destroy documents and the time is after the regulatory retention requirements has passed but before the obliged timeframe contractual to the Sponsor, the Sponsor may be contacted to amend the contracted timeframe or provide for the shipment of documents to the Sponsor or their designee.

### Procedures for Storing Paper-Based Research Documentation

1. Storage Boxes shall be durable and labeled on the outside in easily readable markings with the following suggested documentation:
   1. “Research Documentation Storage” (or similar identifying mark)
   2. Sponsor
   3. Protocol Number
   4. Dates of Study
   5. Box “X” of “Y” (i.e. “Box 1 of 3”)
   6. “Do Not Destroy Before” Date (with reference to the destruction policy)
2. If space in the box is an issue, it is acceptable to recycle the binders from CRFs or separate source document binders. It is not preferable to break down the regulatory binders due to the potential of disrupting the integrity of the documents and the order in which they exist.
3. Storage area shall be secure and not conducive to physical harm to the records or unauthorized access. Examples are as follows:
   1. Adequate prevention from water damage,
   2. Limited access to research and administrative staff only.
4. In the event any records are moved off-site, the storage conditions and security shall be at least similar to those of Investigative Site.
   1. A record of where the boxes are located should be kept by the research staff.
5. If a single study has multiple boxes, the boxes should be kept proximal to each other.

# Research Staff Training

## Policies on Training for Research Staff:

Policy Number: SOPR-RST-100.V1

Effective Date: July 10, 2016

**PURPOSE:** To outline activities required for training for research staff at Investigative Site.

**POLICIES:**

It is the policy atConduct Clinical Trials to train or provide training for all research staff on sponsor protocols, FDA regulations, Good Clinical Practices (GCP), ICH Guidelines, Safety Training and any other applicable training.

Prior to working at Investigative Site, staff will:

* + - 1. Obtain certification in Good Clinical Practices.

Prior to working on any portion of the protocol, staff will:

1. Attend protocol training; it is desirable that at least one or two representatives from the research center attend any investigator meetings. If this is not possible, staff should not begin enrolling subjects until applicable training from the sponsor has occurred.

Prior to completing Case Report Forms, research staff will:

1. Complete any electronic data capture (EDC) training that may be required by the sponsor.

Prior to doing study visits with subjects, staff will:

1. Complete any applicable state certifications and licenses (Healthcare Assistant Certificate, etc)

Prior to shipping dangerous goods, staff will:

1. Complete appropriate Mayo Medical Laboratories Dangerous Goods training and receive appropriate certification(s). http://test.mayomedicallaboratories.com/education/online/dangerousgoods/training.html

Enrolling Staff and Family Members in Trials

## Policies on Enrolling Staff and Family Members in Trials.

Policy Number: SOPR-ESF-100.V1

Effective Date: July 10, 2016

**PURPOSE:** To outline policies on staff and family members in clinical trials.

**POLICIES:**

It is the policy at Conduct Clinical Trials and Investigative Site is not to enroll staff or family members of staff into clinical trials being conducted at Investigative Site. This policy is in place to ensure confidentiality of staff and their family members as well as prevent coercion in the trial.